Daxas® (roflumilast) Tablets
NDA 22-522

Pulmonary-Allergy Drugs Advisory Committee Meeting

April 7, 2010

Introduction

Lisa Travis, MS, RAC

Director, Regulatory Affairs
Forest Research Institute, Inc.

Roflumilast

- New oral once daily anti-inflammatory therapy for COPD
- Potent, selective PDE-4 inhibitor chemically and pharmacologically distinct from other COPD therapies
- Targets key proinflammatory mediators underlying the pathogenesis of COPD and associated exacerbations
- Demonstrated clinical safety and effectiveness in patients with COPD

COPD=chronic obstructive pulmonary disease; PDE-4=phosphodiesterase-4.

Roflumilast
Proposed Indication Statement

Roflumilast is indicated for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

Roflumilast
Proposed Indication Statement

Roflumilast is indicated as maintenance treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbations.

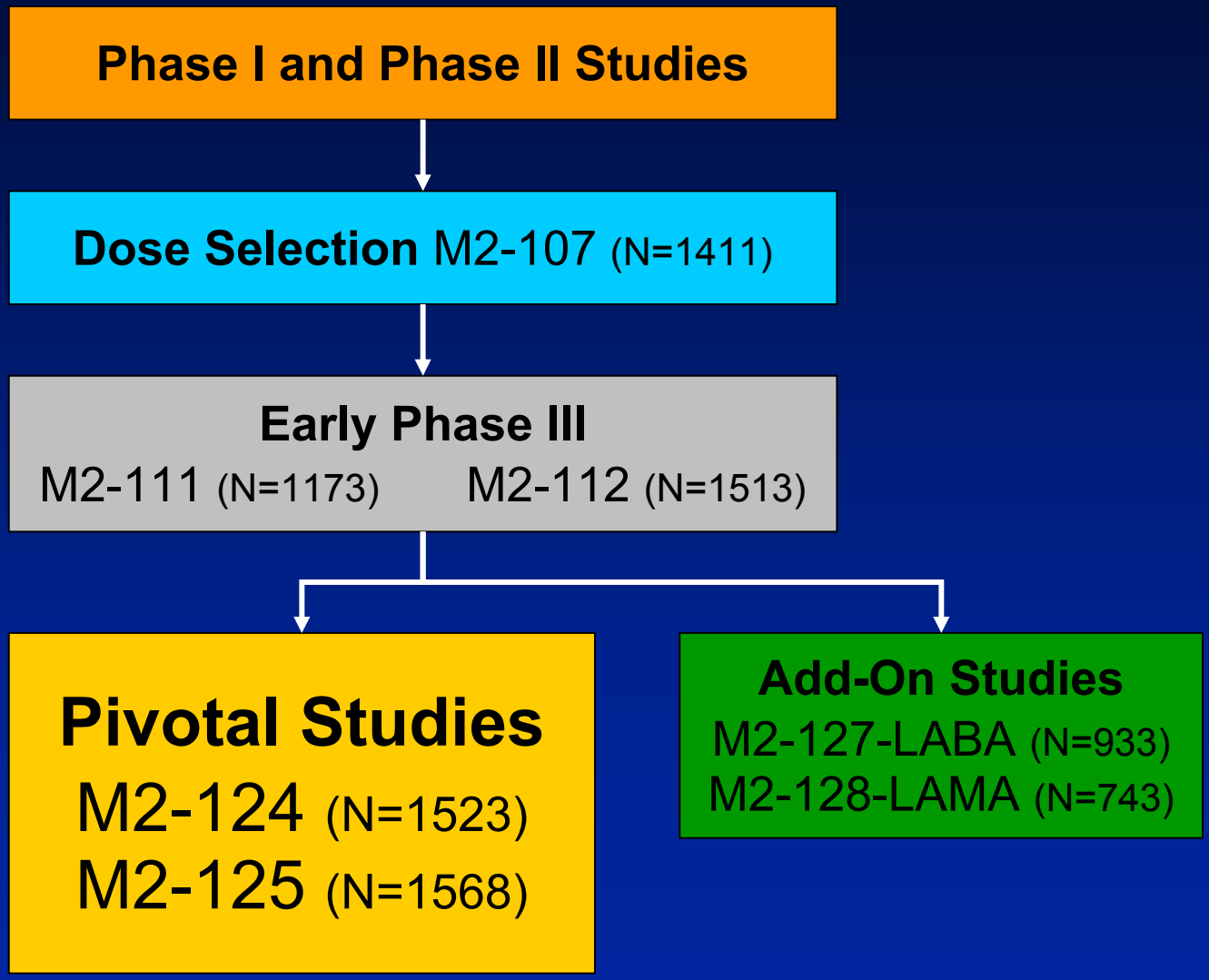
FDA Draft Guidance for Industry: COPD *(1/2)*

- **Chronic Bronchitis**
  - **...a therapy can target subsets of the disease, such as chronic bronchitis.**
- **Exacerbations**
  - **...several types of drugs that can be developed for COPD based on whether the drug is intended to improve airflow obstruction, provide symptom relief, modify or prevent exacerbations...a drug may affect only one aspect of the disease or that it may act on many.**
  - **Therapeutic drugs that...prevent COPD exacerbations will provide meaningful benefit to patients.**

FDA Draft Guidance for Industry: COPD *(2/2)*

- **Efficacy**
  - **...two confirmatory Phase 3 studies should be conducted to establish efficacy...to modify or prevent exacerbations.**

Roflumilast COPD Clinical Program



Presentation Overview

Introduction	***Lisa Travis, MS, RAC*** Director, Regulatory Affairs Forest Research Institute, Inc.
Medical Need & Pharmacology	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Roflumilast Investigator
Dose Finding & Efficacy	***Klaus F. Rabe, MD, PhD*** Professor of Medicine, Department of Pulmonology Leiden University Medical Center Roflumilast Investigator
Safety	***Marco Taglietti, MD*** Chief Medical Officer Forest Research Institute, Inc.
Risk/Benefit & Clinician Perspective	***James Donohue, MD*** Chief of Pulmonary Medicine University of North Carolina, Chapel Hill Roflumilast Investigator

Experts Available to Advisory Committee

Neil Barnes, MD, FRCP
Professor of Respiratory Medicine
London Chest Hospital
Barts and the London School of Medicine and Dentistry
Barts and the London NHS Trust
London, England

Peter Calverley, MD
Professor of Respiratory Medicine
University of Liverpool
Honorary Consultant Physician
University Hospital Aintree
Liverpool, England

Phillip Schein, MD
Visiting Professor, Oxford University
Former Chair, FDA Oncologic Drugs Advisory Committee

Gary Koch, PhD
Professor of Biostatistics
Department of Biostatistics
The University of North Carolina at Chapel Hill
Gillings School of Global Public Health
Chapel Hill, North Carolina

William B. White, MD
Professor, Department of Medicine
University of Connecticut Health Center
Farmington, Connecticut

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COPD & Roflumilast Pharmacology

Stephen Rennard, MD, FCCP

Professor of Internal Medicine
University of Nebraska Medical Center

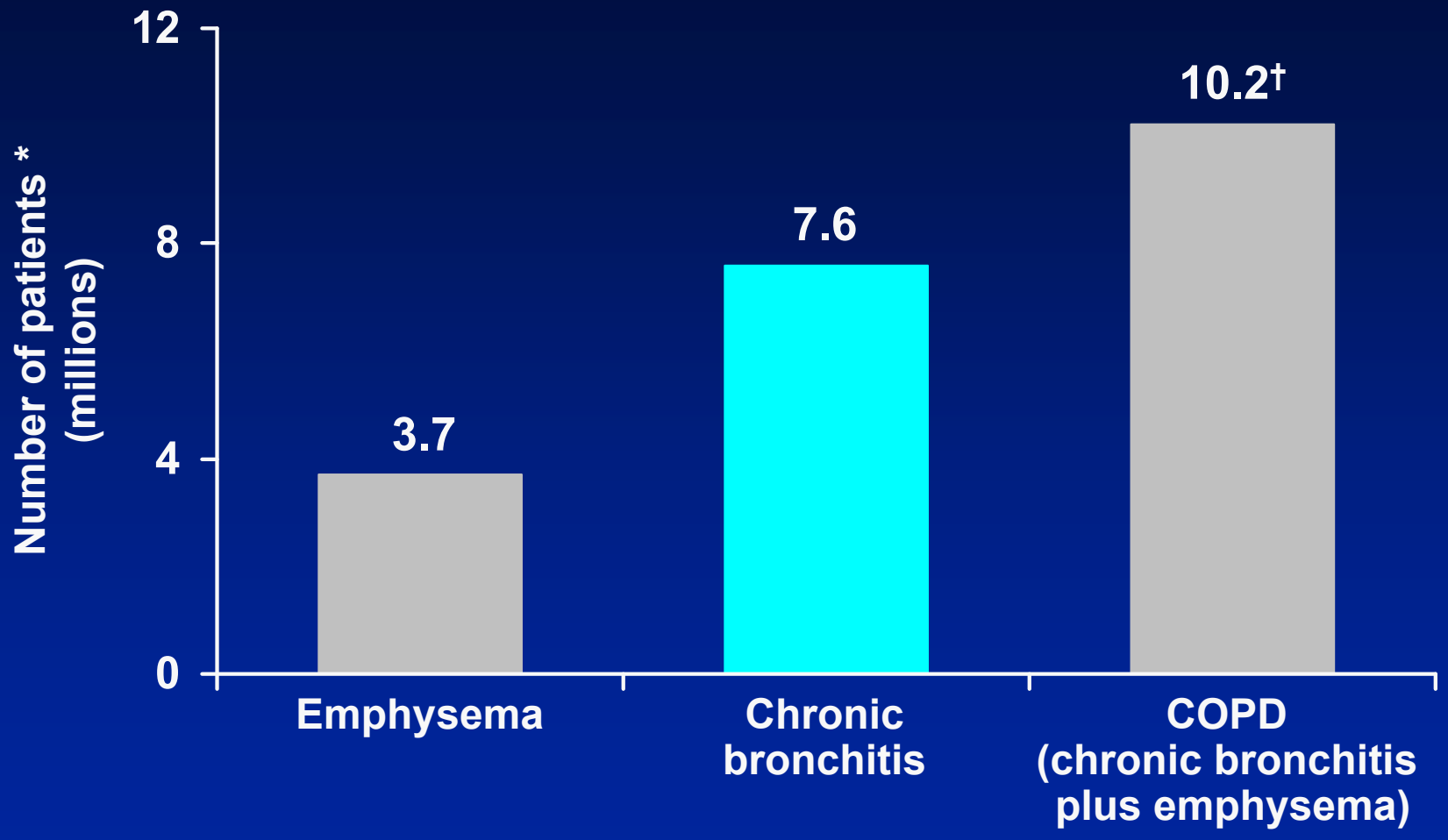
Roflumilast Investigator

Prevalence and Impact of COPD

Prevalence[1]	~12-24 million
Emergency Department visits[2]	~2 million
Hospitalizations[2]	661,000
Deaths[3]	124,583

[1] Healthy People 2010. Progress Review: Respiratory Diseases. May 22, 2008.
[2] Heron M et al. Natl Vital Stat Rep. 2009;57:1-134;3. American Lung Association
[3] Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality. April 2009.

Chronic Bronchitis Is a Subset of COPD[1]



* Adults ≥18 years of age

† Note: COPD totals take into account the overlap of persons with both diseases.

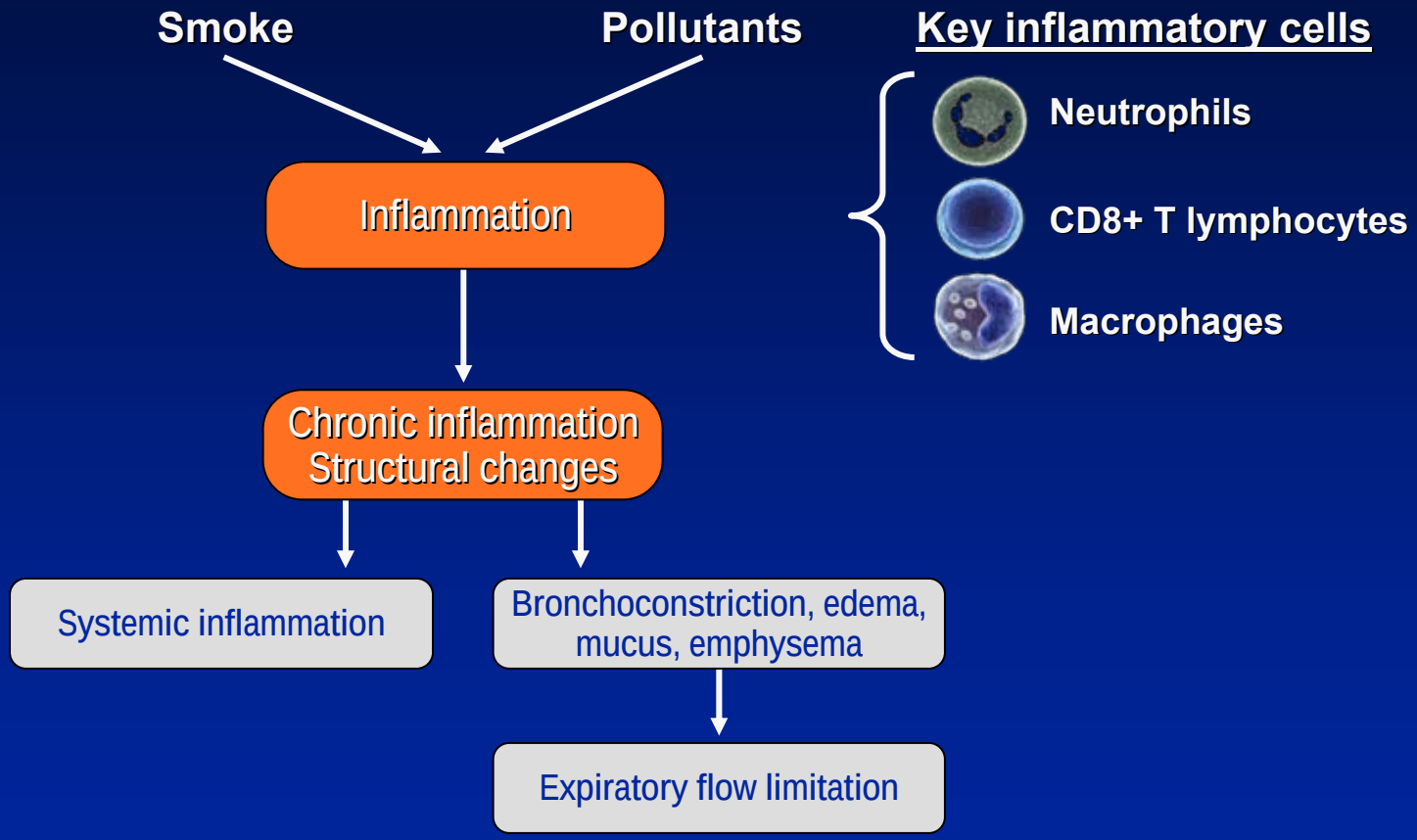
[1] American Lung Association Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality. April 2009.

Exacerbations

- Event: *characterized by a change in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management*[1]
- Health care burden
- Mortality
- Risk factors
  - Previous exacerbations
  - Poor lung function
  - Chronic bronchitis

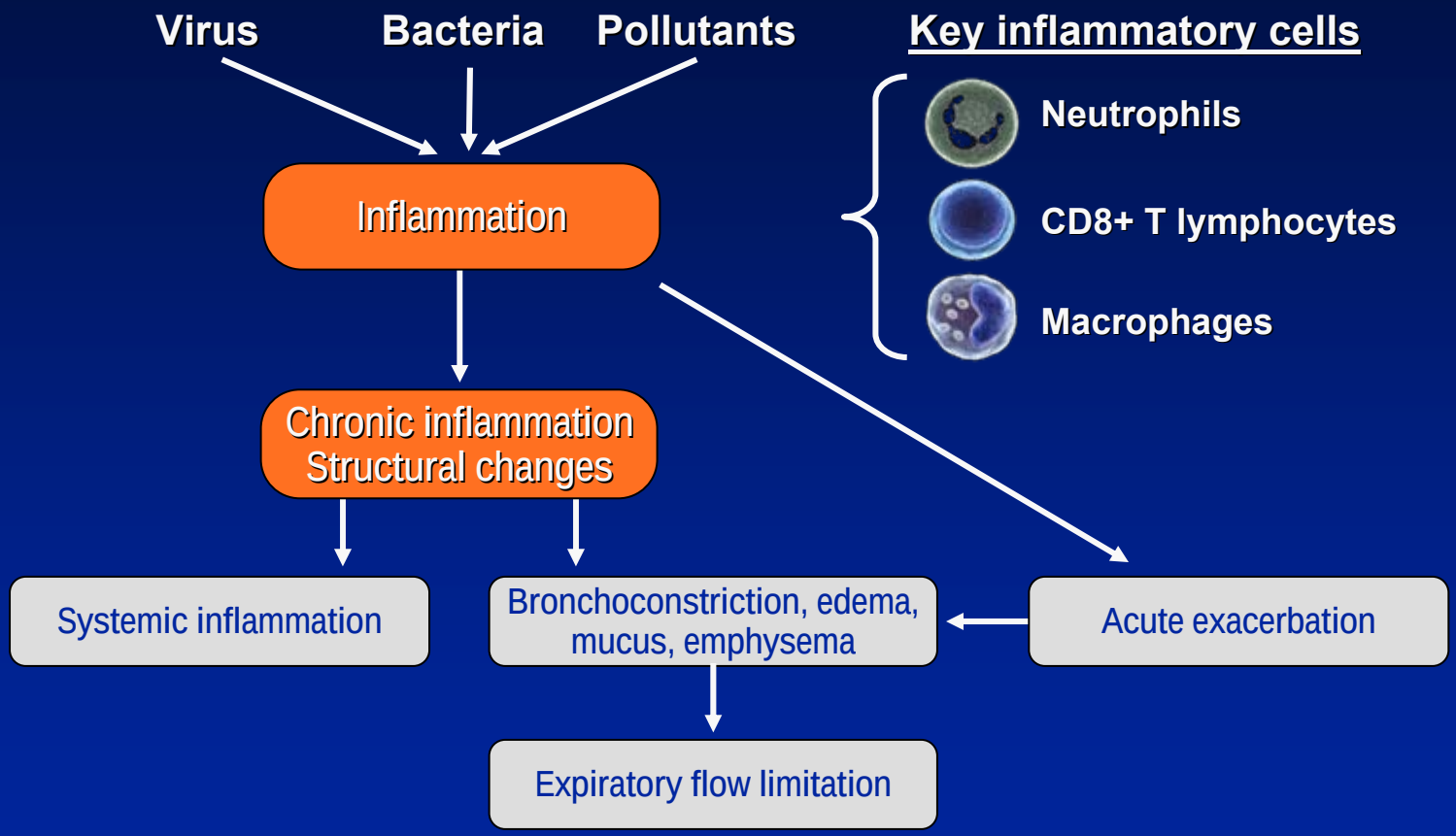
[1] Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Celli and MacNee ERJ 23: 932-46, 2004

Inflammation is a Core Component of the Pathophysiologic Changes in COPD



Adapted from Wedzicha JA, Seemungal TA. *Lancet.* 2007;370:786-796; Vethove KJ et al. *Biomarkers.* 2009;14:523-528; Groenewegen KH et al. *Chest.* 2008;133:350-357; Hansel JA, et al. *Lancet.* 2009;374:744-755; Drost EM et al. *Thorax.* 2005;60:293-300; Barnes PJ. Chemokines in COPD. In: Stockley RA, Rennard SI, Rabe K, Celli B, eds. Chronic Obstructive Pulmonary Disease. Oxford, England: Blackwell Publishing; 2007:860.

Inflammation is a Core Component of COPD Exacerbations



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Direct Patient Quotes About Exacerbations[1]

(From the FDA co-initiated EXACT-PRO patient focus groups)

- I get short of breath. I can't move around much.
- It just feels like there's a very, very tight belt around my chest.
- It cuts you at the knees.
- I was coughing, dry coughing, very bad. And here like I tell you it hurts.
- It kind of makes you edgy…because your breathing is not normal so you get palpitations.
- I was afraid.

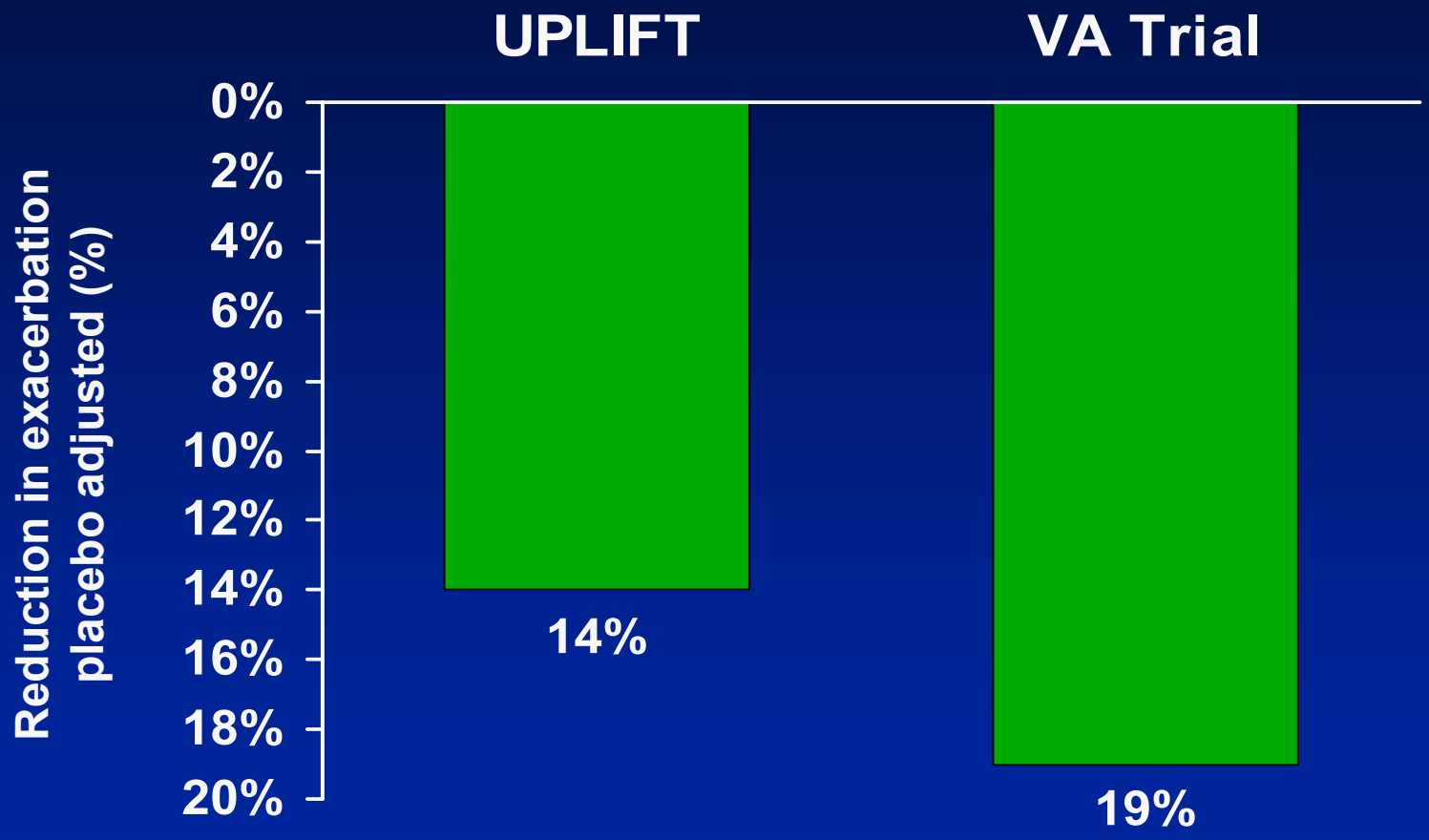
[1] From the FDA co-sponsored EXACT-PRO focus group transcripts, courtesy N. Leidy, UBS

Therapy at Each Stage of COPD

I: Mild	II: Moderate	III: Severe	IV: Very Severe
• $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted	• $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ predicted	• $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < 50\%$ predicted	• $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure
Active reduction of risk factor(s); influenza vaccination → ***Add*** short-acting bronchodilator (when needed) →			
	Add regular treatment with one or more long-acting bronchodilators (when needed); ***Add*** rehabilitation		
		Add inhaled glucocorticosteroids if repeated exacerbations	
			Add long term oxygen if chronic respiratory failure. ***Consider*** surgical treatments

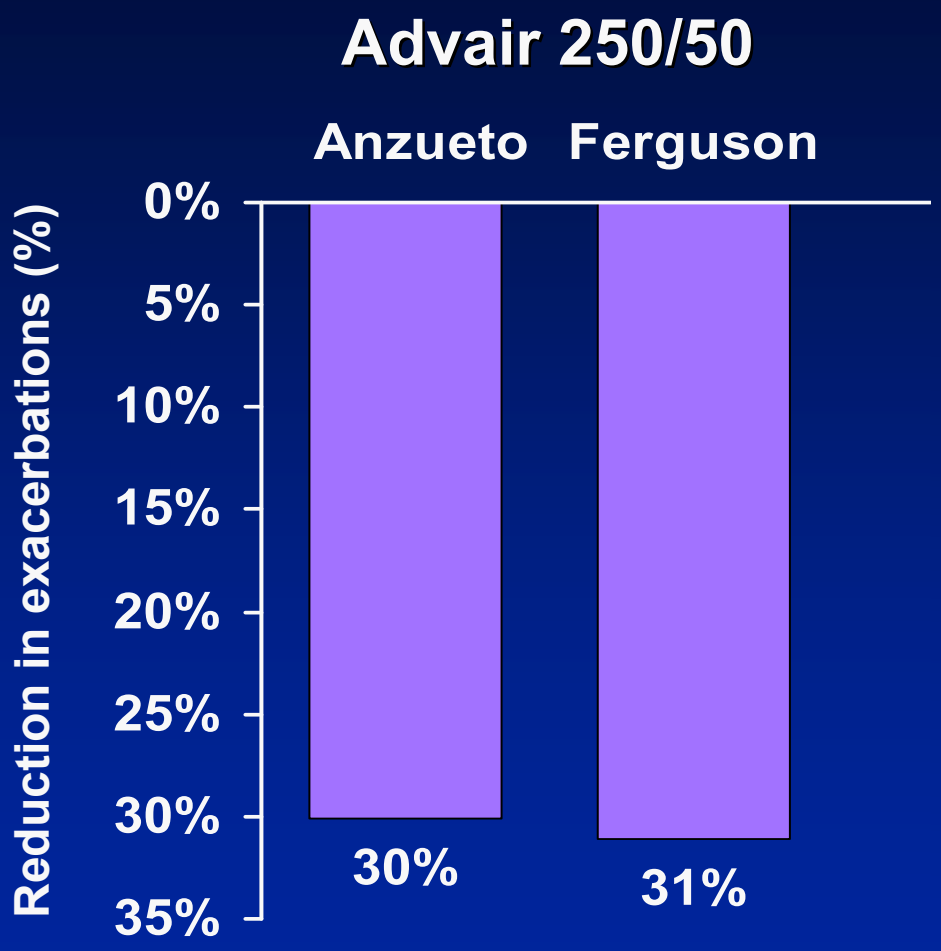
Adapted with permission from *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2008. Available from: http://www.goldcopd.org; US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance: COPD. November 2007.

Effect Size of Currently Approved Therapies for COPD Exacerbation Reduction: Spiriva



Tashkin et al, 2008; FDA Spiriva Briefing Book November 2009

Advair Reduces COPD Exacerbations



* Not approved in USA

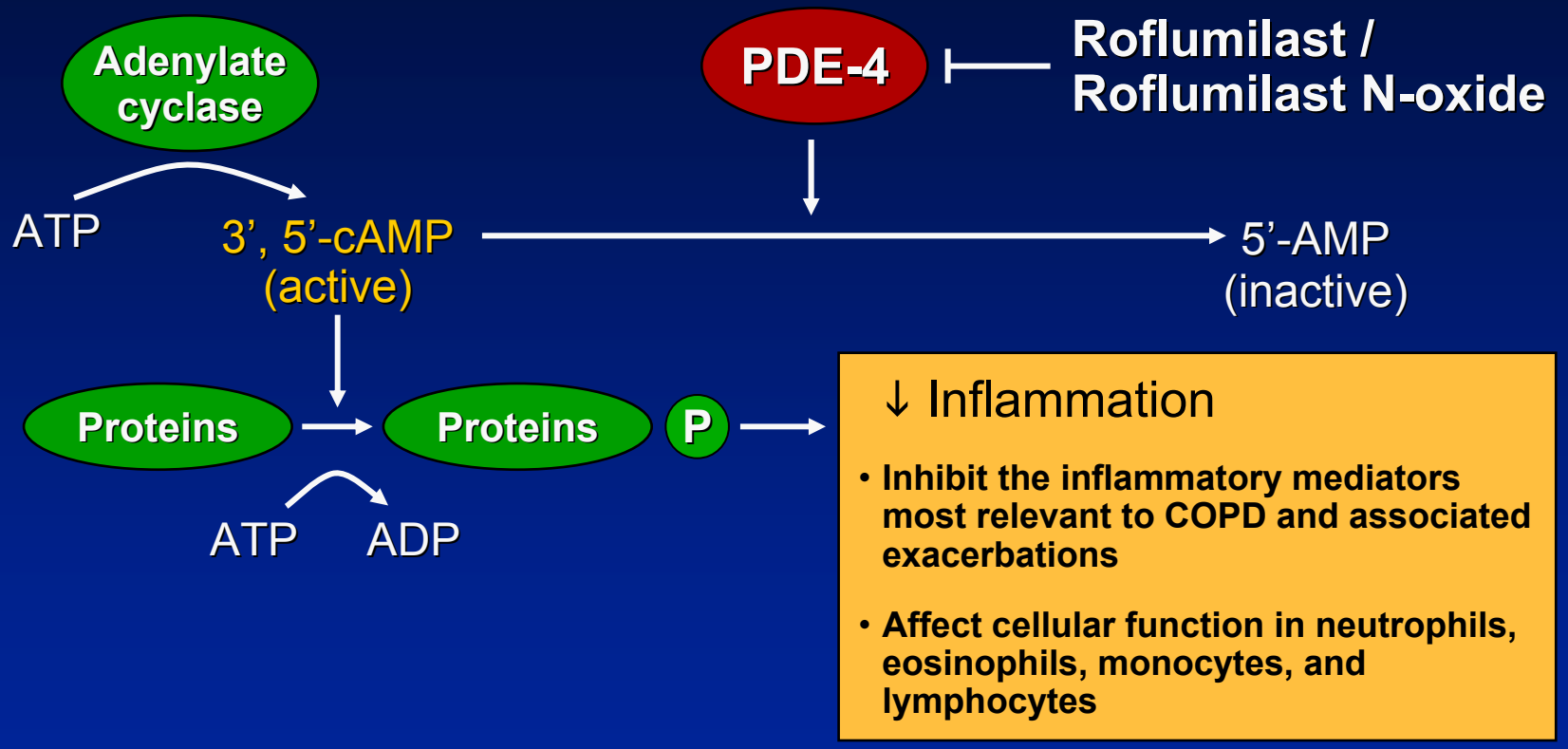
Anzueto et al J COPD 2009; Ferguson et al Resp Med 2009: Calverley et al LANCET 2003; Calverley et al NEJM 2007

Summary: Chronic Obstructive Pulmonary Disease

- Common
- Major health problem
- Exacerbations
  - Current therapies: 14-25% reduction
  - Additional therapy needed

Pharmacology of Roflumilast and Active N-oxide Metabolite

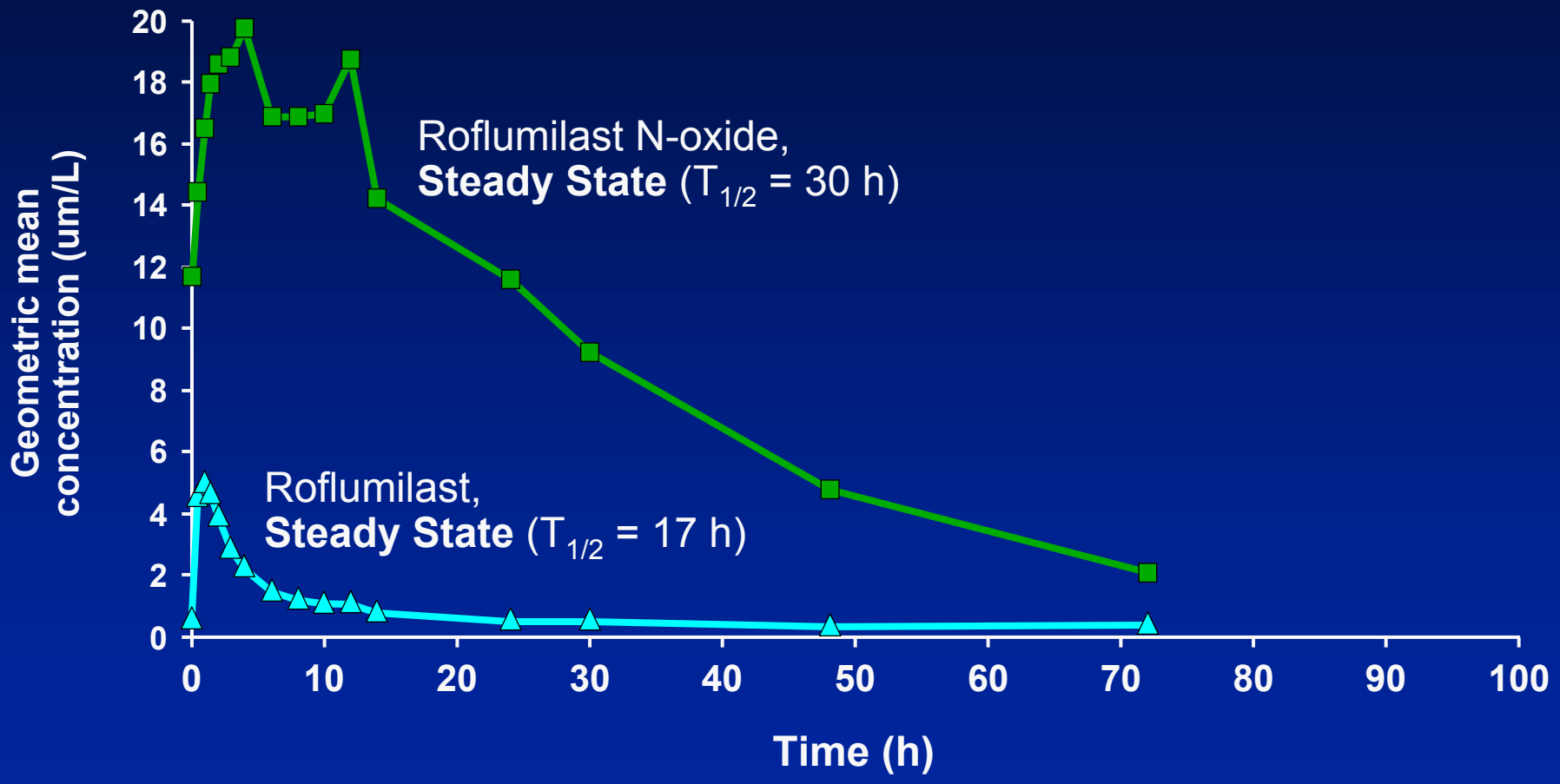
Rationale for Roflumilast to Treat COPD



ADP=adenosine diphosphate; AMP=adenosine monophosphate; ATP=adenosine triphosphate; PKA=protein kinase; Th1=type 1 T helper cell; Th2=type 2 T helper cell.

Adapted from Tenor H et al. Phosphodiesterase-4 inhibitors in the treatment of COPD. In: Stockley RA, Rennard SI, Rabe K, Celli B, eds. *Chronic Obstructive Pulmonary Disease.* Oxford, England: Blackwell Publishing; 2007:708.; Field SK. *Expert Opin Investig Drugs.* 2008;17:811-818.

Pharmacokinetic Profile of Roflumilast and RNO from Steady State



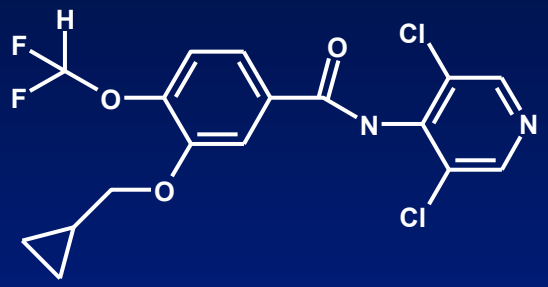
Pharmacokinetic Summary of Roflumilast and Roflumilast N-oxide

- No clinically relevant drug interactions
  - No interactions:
    - albuterol
    - enoxacin
    - theophylline
    - sildenafil
    - warfarin
    - erythromycin
    - formoterol
    - budesonide
    - montelukast
    - digoxin
    - midazolam
    - ketoconazole
  - More than 80% decrease in exposure to roflumilast:
    - rifampicin* (and other CYP3A4 inducers)

* Also known as rifampin

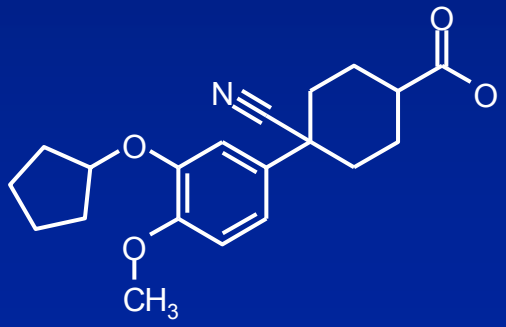
Roflumilast is Distinct from Cilomilast and Theophylline

ROFLUMILAST



- Highly selective PDE4 inhibitor

CILOMILAST



- Inhibits PDE4D > other PDE4

THEOPHYLLINE

- Non-selective PDE inhibitor
- Acts on multiple additional targets

Roflumilast: Pharmacology Conclusion

- Anti-inflammatory
- Oral
- Clinical pharmacokinetic profile supports once-daily dosing
- No clinically important drug-drug interactions

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Dose Finding & Efficacy

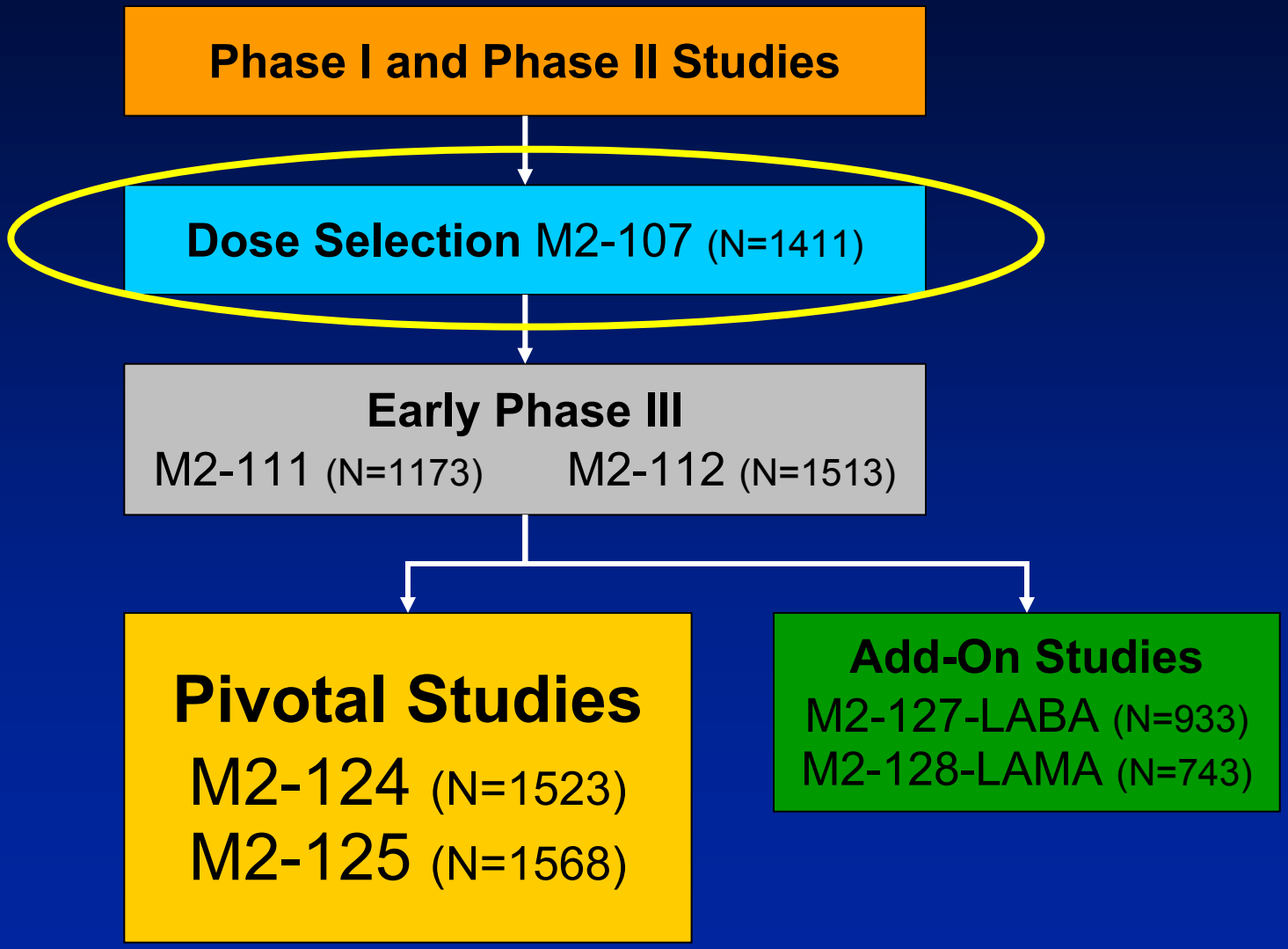
Klaus F. Rabe, MD, PhD

Professor of Medicine, Department of Pulmonology
Leiden University Medical Center

Roflumilast Investigator

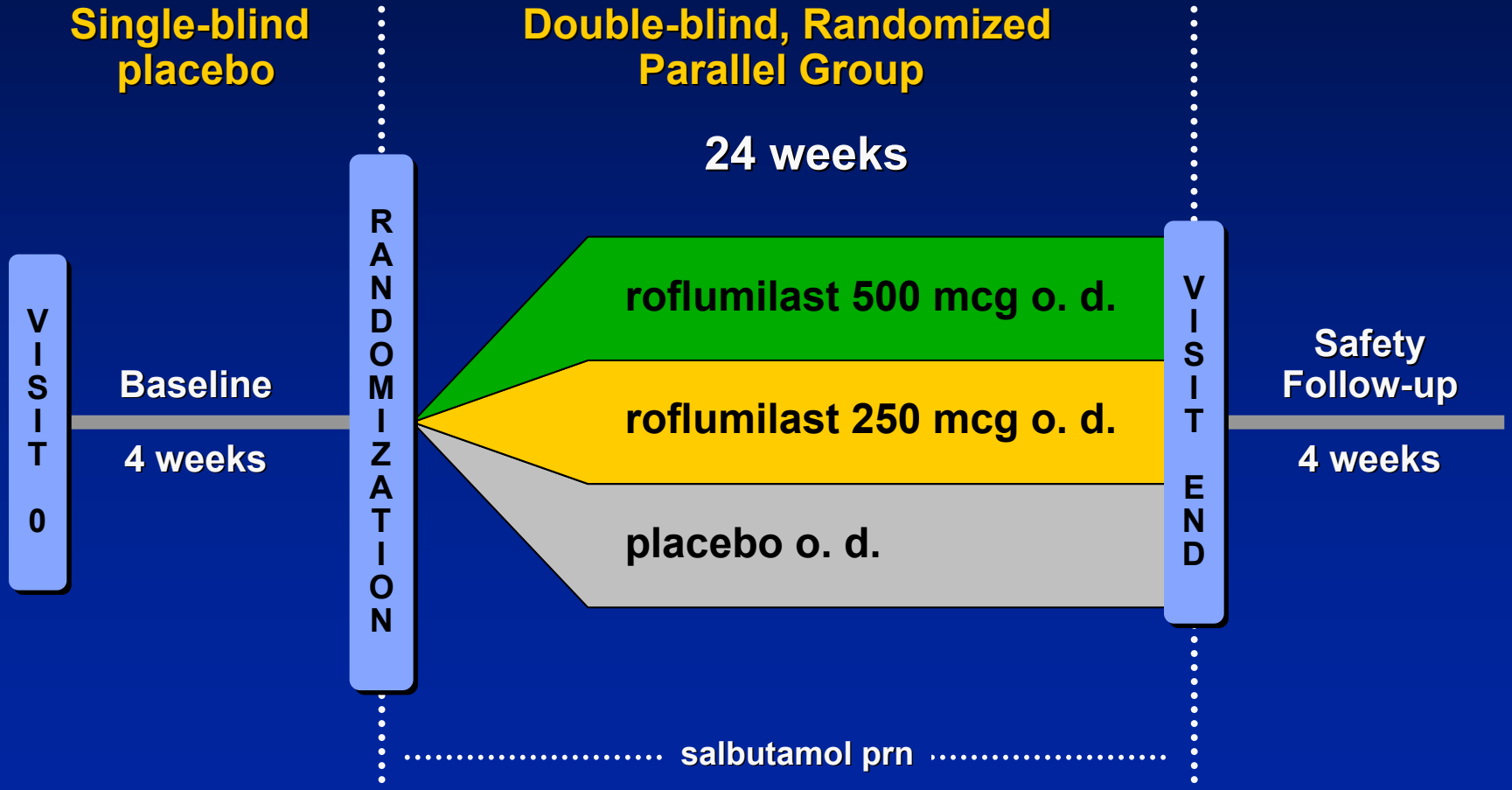
Dose Finding

Roflumilast COPD Clinical Program



M2-107: Dose Response Study

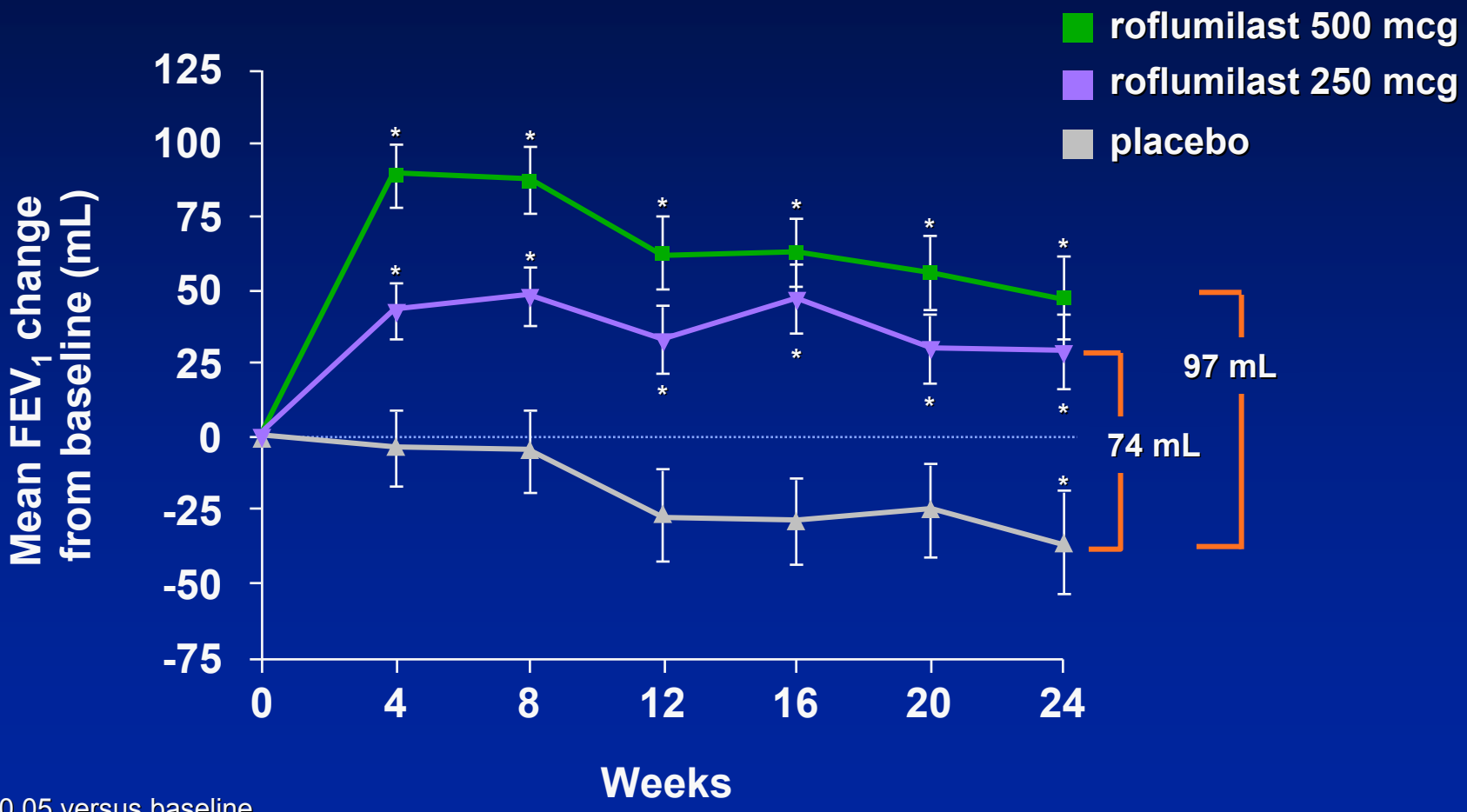
- Patients with moderate and severe COPD
- 1,411 patients randomized



Stable SAMA use allowed. All other respiratory meds discontinued 4 weeks before randomization

M2-107

Primary End Point: Significant Improvement in Post-bronchodilator FEV_1



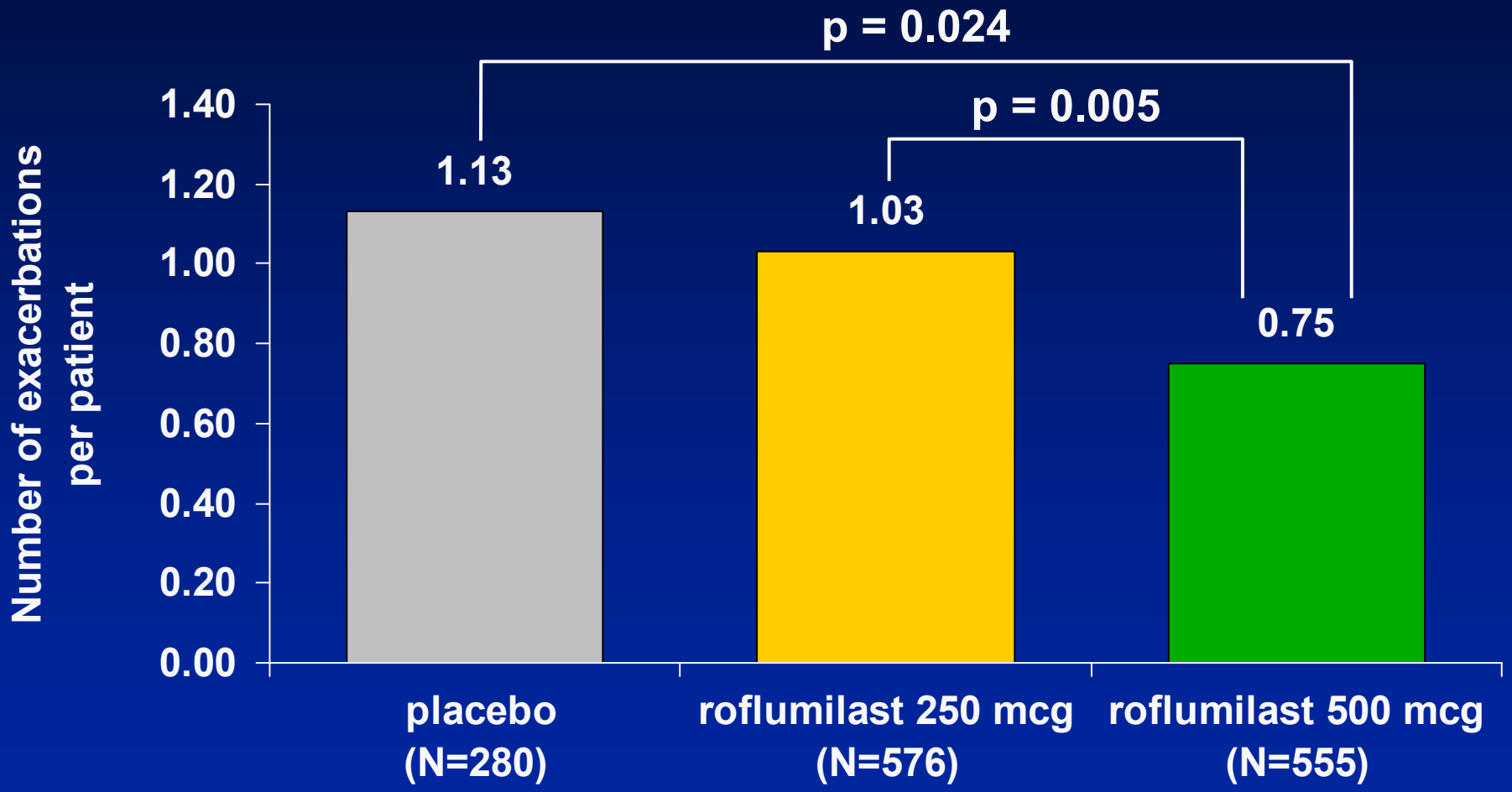
p<0.05 versus baseline

T-Figure 3 p.99 M2-107 report body-2

Rabe et al. Lancet. 2005.

M2-107 Dose Response Study

Exacerbations*: Largest Reduction Observed at 500 mcg Dose



* Mild, moderate, and severe exacerbations

T-Figure 5 p.115 M2-107 report body-2

Rabe et al. Lancet. 2005.

M2-107 Dose Range Finding Study

Dose Response for Selected Adverse Events

	% of Patients		
	placebo (N=280)	rof250 (N=576)	rof500 (N=555)
Any AE	62.1	66.3	66.7
Serious AEs	7.5	7.1	9.5
AEs leading to premature discontinuation	8.2	9.7	14.8
Selected AEs (MedDRA preferred term)			
Diarrhea	2.1	4.9	9.0
Nausea	0.7	2.8	4.9
Abdominal pain	0.7	0.3	2.2
Weight decrease	0.0	1.0	2.3

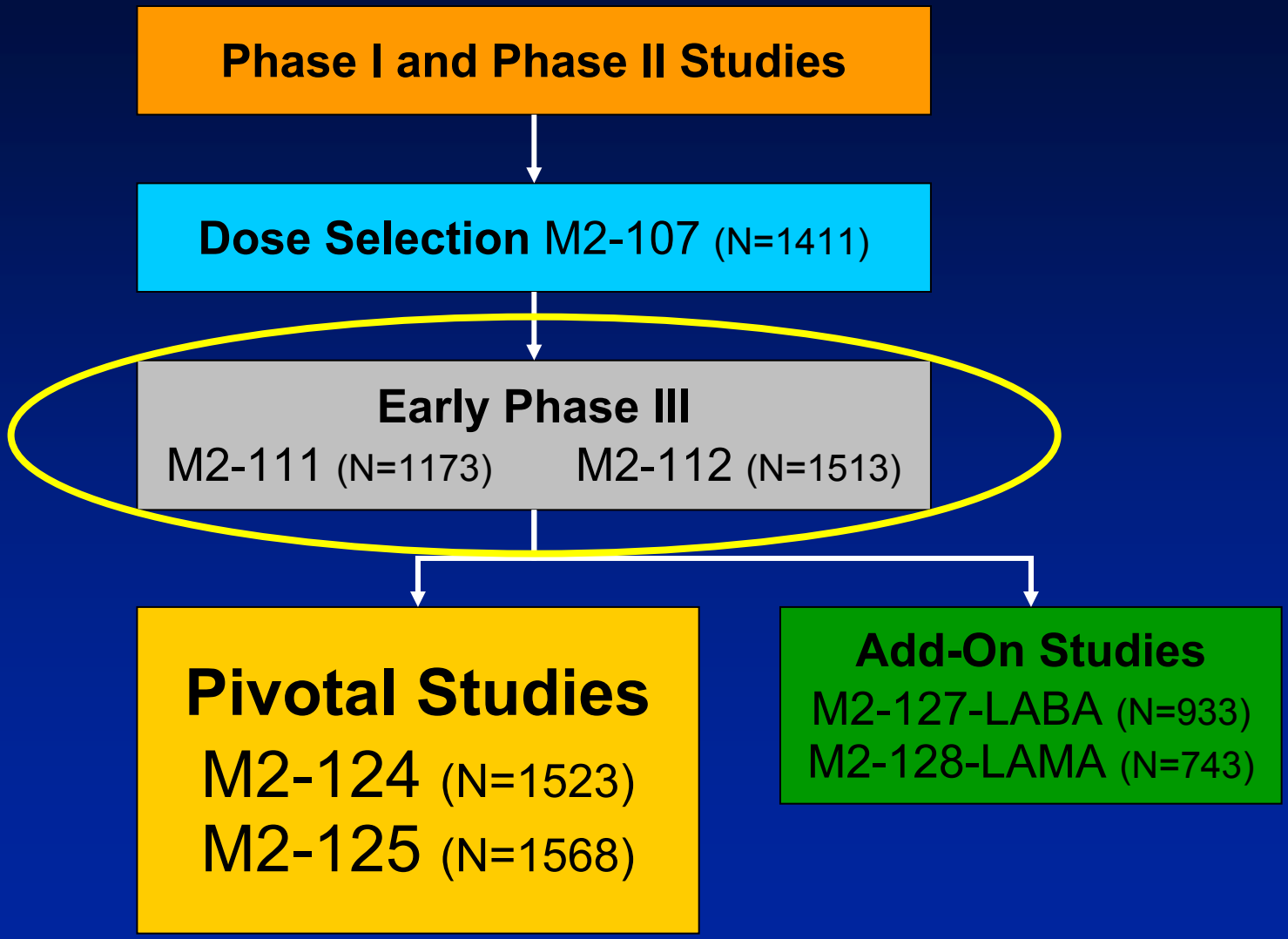
Roflumilast 500 mcg Dose was Selected for Development

Summary

- Dose response relationship observed for FEV_1 and exacerbations supporting selection of the 500 mcg dose
- Safety and tolerability of both doses was acceptable
  - Most frequent events were nausea, diarrhea and headache: higher for 500 mcg dose

Studies Leading to Selection of Target Population

Roflumilast COPD Clinical Program



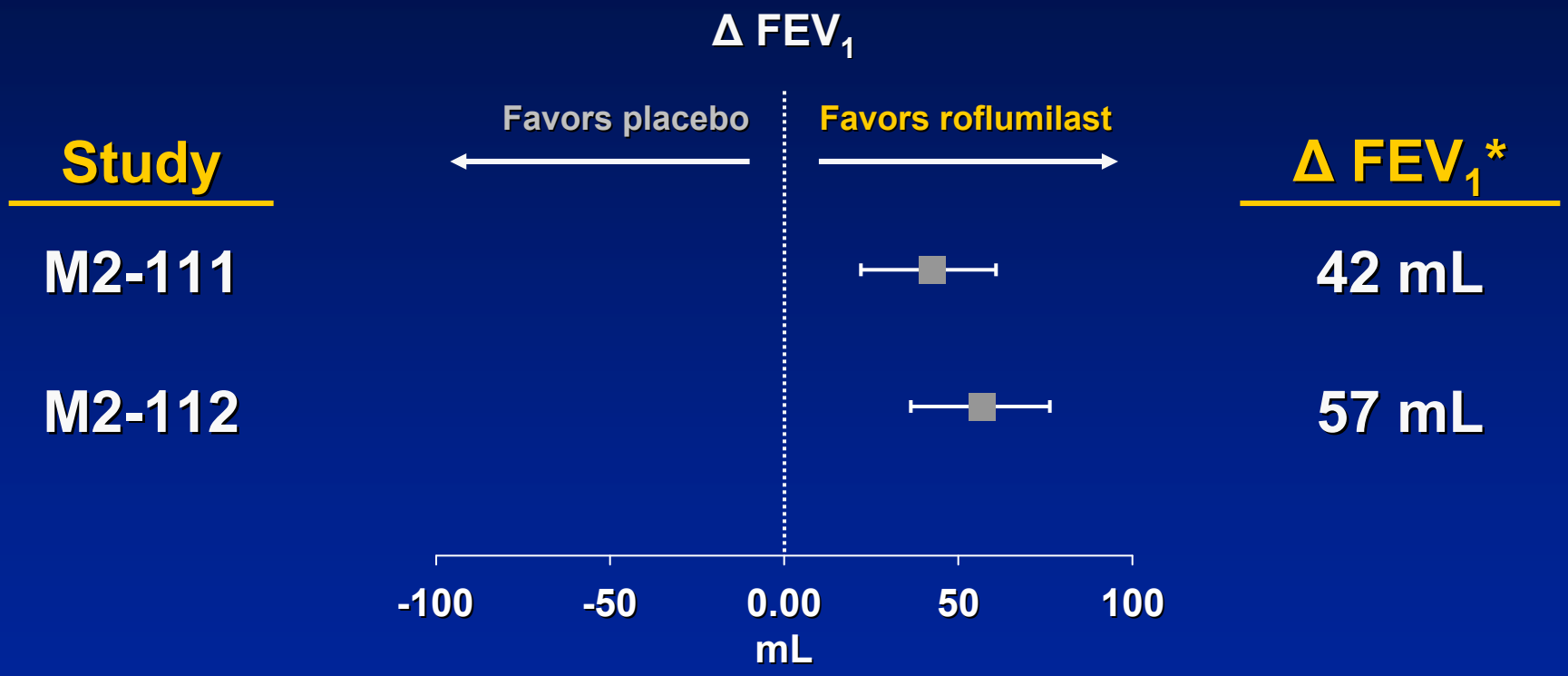
M2-111 / M2-112

Key Study Characteristics

- 52 week, randomized, double-blind, parallel group roflumilast 500 mcg daily vs. placebo
  - M2-111 N = 1173
  - M2-112 N = 1513
- Severe to very severe COPD (chronic bronchitis and/or emphysema)
  - FEV_1 ≤50%;
  - FEV_1/FVC <70%
- Primary End Points
  - Pre-bronchodilator (M2-111) or Post-bronchodilator FEV_1 (M2-112)
  - Rate of moderate or severe exacerbations
    - Moderate—oral/parenteral corticosteroid-treated
    - Severe—associated with hospitalization or death
- Concomitant Medications
  - ICS, SABAs, SAMAs
  - No LABAs or LAMAs

M2-111 / M2-112

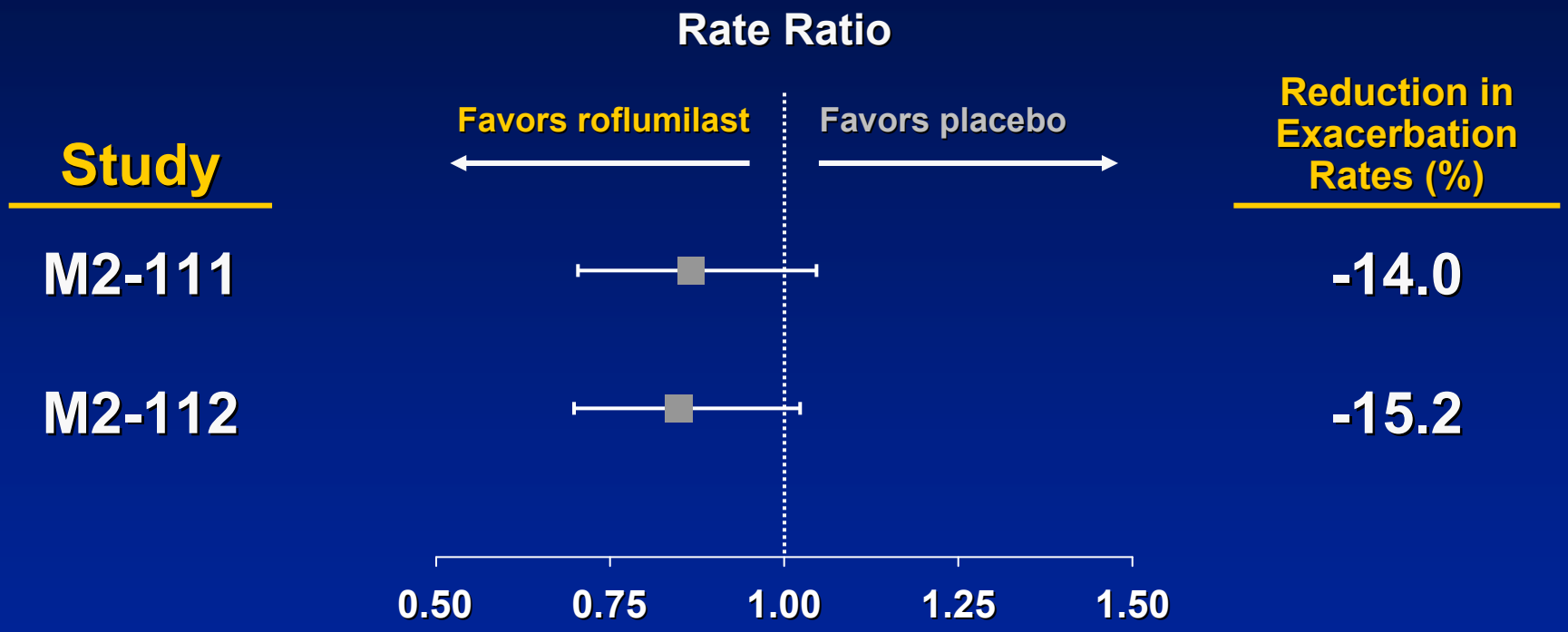
Primary End Point: Significant Improvement in Pre-bronchodilator FEV_1



* Placebo Adjusted. Repeated measure ANCOVA was used with unstructured covariance matrix to estimate mean. Means are adjusted for baseline measurements.

M2-111 / M2-112

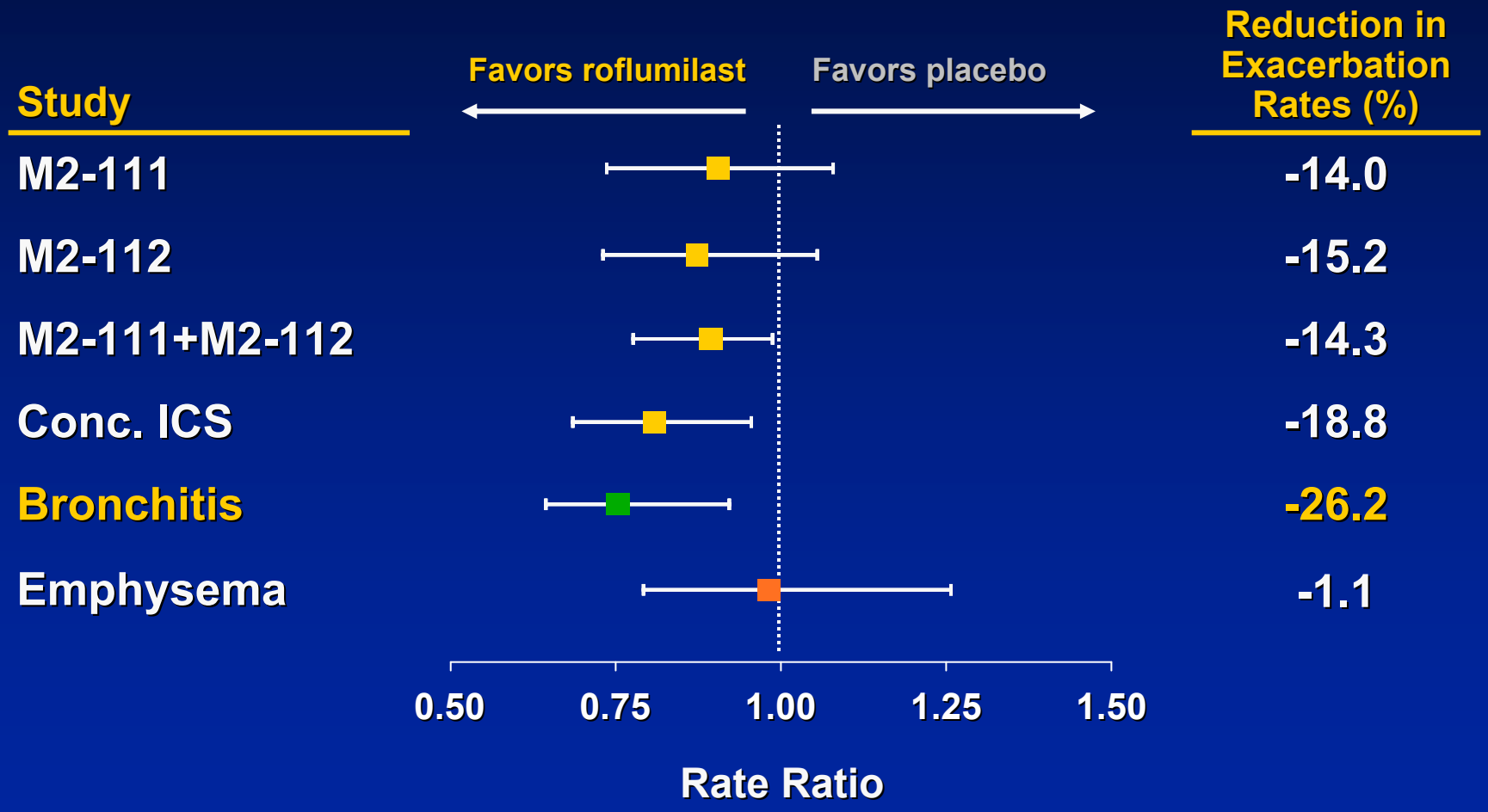
Rate Ratio in Moderate or Severe COPD Exacerbations Favors Roflumilast



Exacerbation rates were based on a Poisson regression model corrected for treatment exposure and overdispersion.

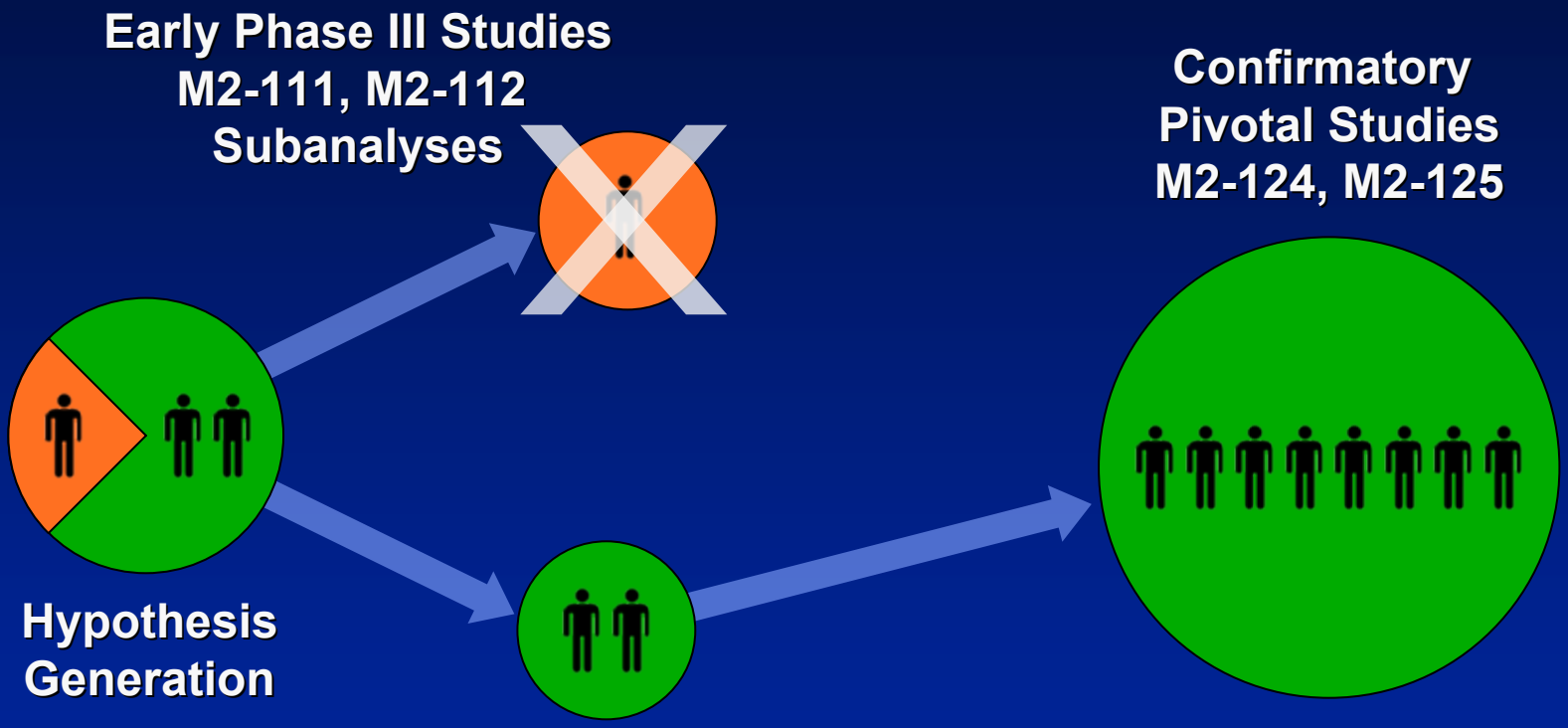
M2-111 / M2-112

Rate Ratio in Moderate or Severe COPD Exacerbations Favors Roflumilast



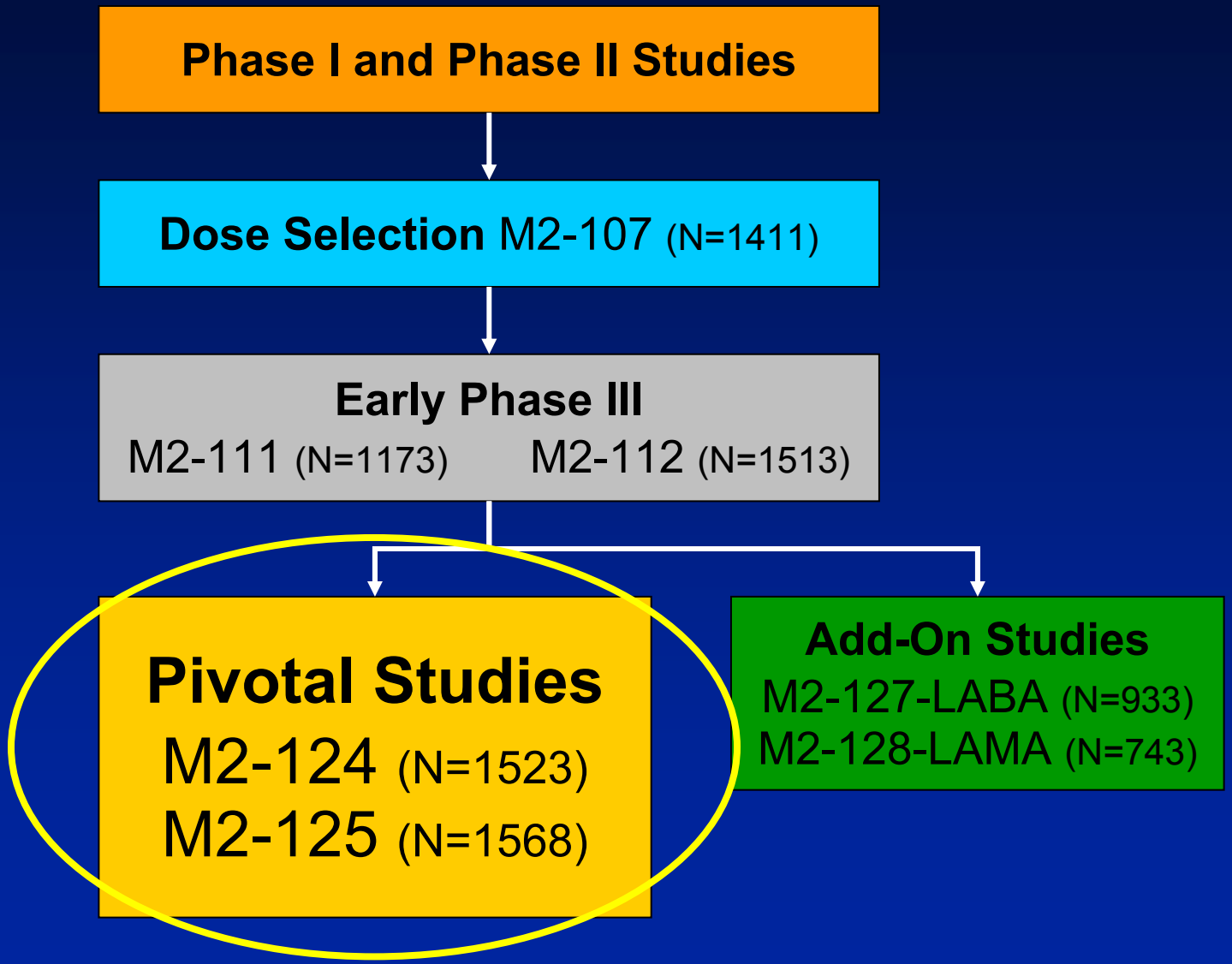
Exacerbation rates were based on a Poisson regression model corrected for treatment exposure and overdispersion

Evolution of Roflumilast Program
Identification of Target COPD Population



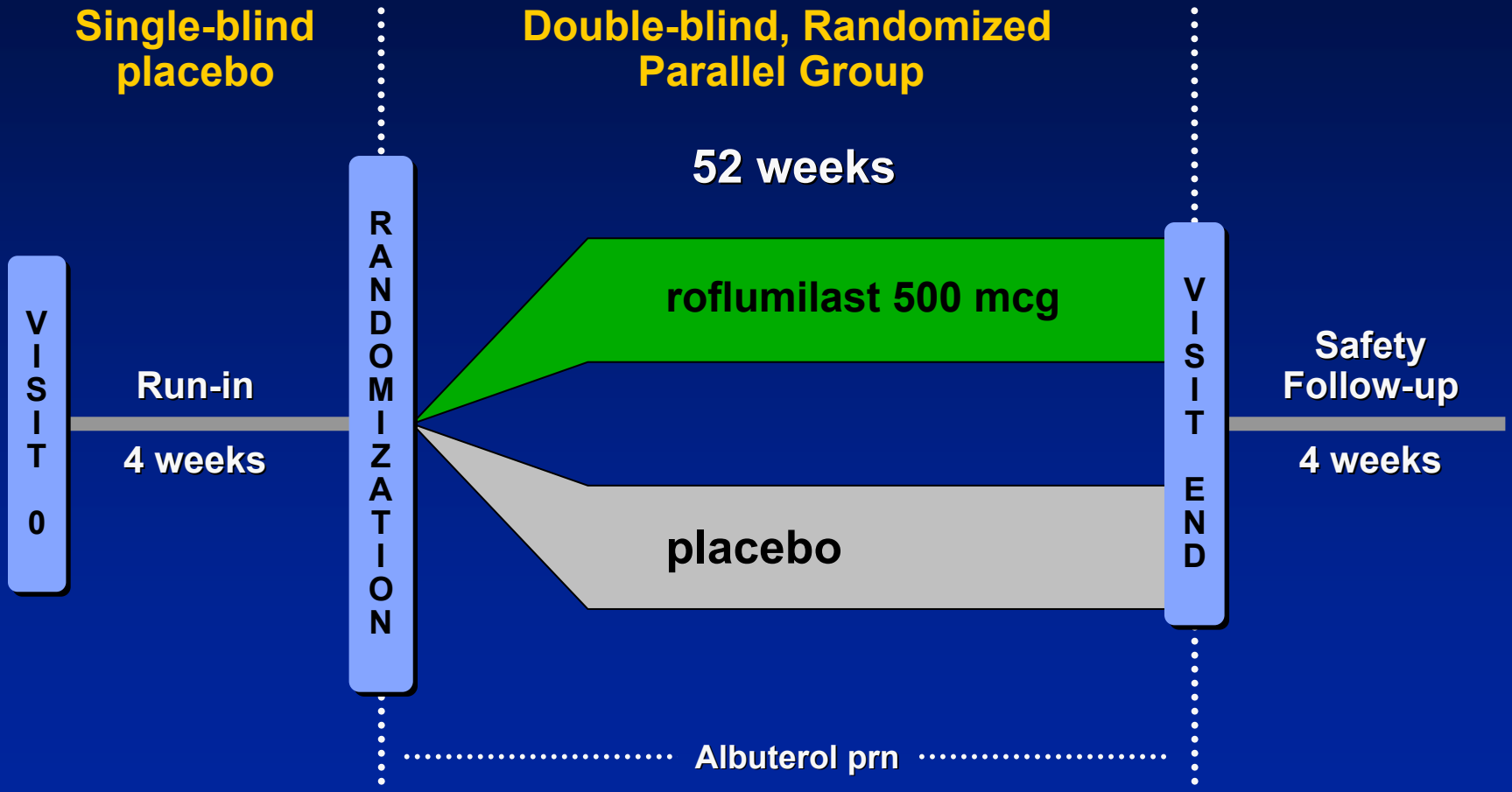
Treatment of COPD Associated With Chronic Bronchitis in Patients at Risk of Exacerbations

Roflumilast COPD Clinical Program



M2-124 / M2-125

Roflumilast Pivotal Studies: Design Features



Eligibility criteria include: COPD >12mo, required diagnosis of chronic bronchitis, and a history of previous exacerbations. LABA use allowed, ICS use discontinued at randomization, no LAMA use during study period.

M2-124 / M2-125

Key Inclusion Criteria

Severe to very severe COPD

- ***Chronic bronchitis***
  - ***Chronic productive cough for 3 months in each of the prior 2 years[1]***
- ***Exacerbation history (within 1 year prior to study)***
  - ***At least 1 documented COPD exacerbation requiring systemic corticosteroids, hospitalization, or both***
- **Age >40 years**
- **FEV_1/FVC ratio (post-bronchodilator) ≤70%**
- **FEV_1 (post-bronchodilator) ≤50% of predicted**
- **Current or former smoker with a smoking history of at least 20 pack-years**

[1] As defined by ATS/ERS 2004.

M2-124 / M2-125

Co-primary End Points

- Pre-bronchodilator FEV_1
- Rate of Moderate or Severe Exacerbations

M2-124 / M2-125

Definition of Exacerbation

- COPD exacerbation is an event in the natural course of disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management...

As defined by ATS/ERS 2004, GOLD 2009, Rodriquez-Roisin et al, Chest. 2000.

M2-124 / M2-125

Definition of Exacerbation

- **Moderate:**
  Oral/parenteral corticosteroid-treated
- **Severe:**
  Associated with hospitalization or death

M2-124 / M2-125

Demographics and Baseline Characteristics

	M2-124		M2-125	
	rof500 (N=765)	placebo (N=758)	rof500 (N=772)	placebo (N=796)
Median Age (years)	63	63	64	65
Men (%)	71	71	79	81
Cigarette pack-years	48	46	49	47
Current smoker (%)	48	48	35	35
Body mass index (kg/m^2)	26.4	26.0	25.2	25.4
Ethnic origin				
Black	1	2	1	2
White	96	97	72	71
Other*	2	1	27	27

* Includes Asian and Native American Ethnicities
North America population was >20%
ITT Population

M2-124 / M2-125

Baseline Lung Function and COPD Severity

	M2-124		M2-125	
	rof500 (N=765)	placebo (N=758)	rof500 (N=772)	placebo (N=796)
Pre-bronchodilator FEV_1 (L) (% predicted)	1.07 (34.7)	1.06 (34.6)	0.95 (31.4)	0.98 (32.2)
Reversibility (%)	9.7	10.0	11.7	11.0
Post-bronchodilator FEV_1/FVC (%)	43.3	42.7	41.2	41.3
Severe COPD (%)	64	67	59	60
Very severe COPD (%)	26	24	34	32

North America population was >20%
ITT Population

M2-124 / M2-125

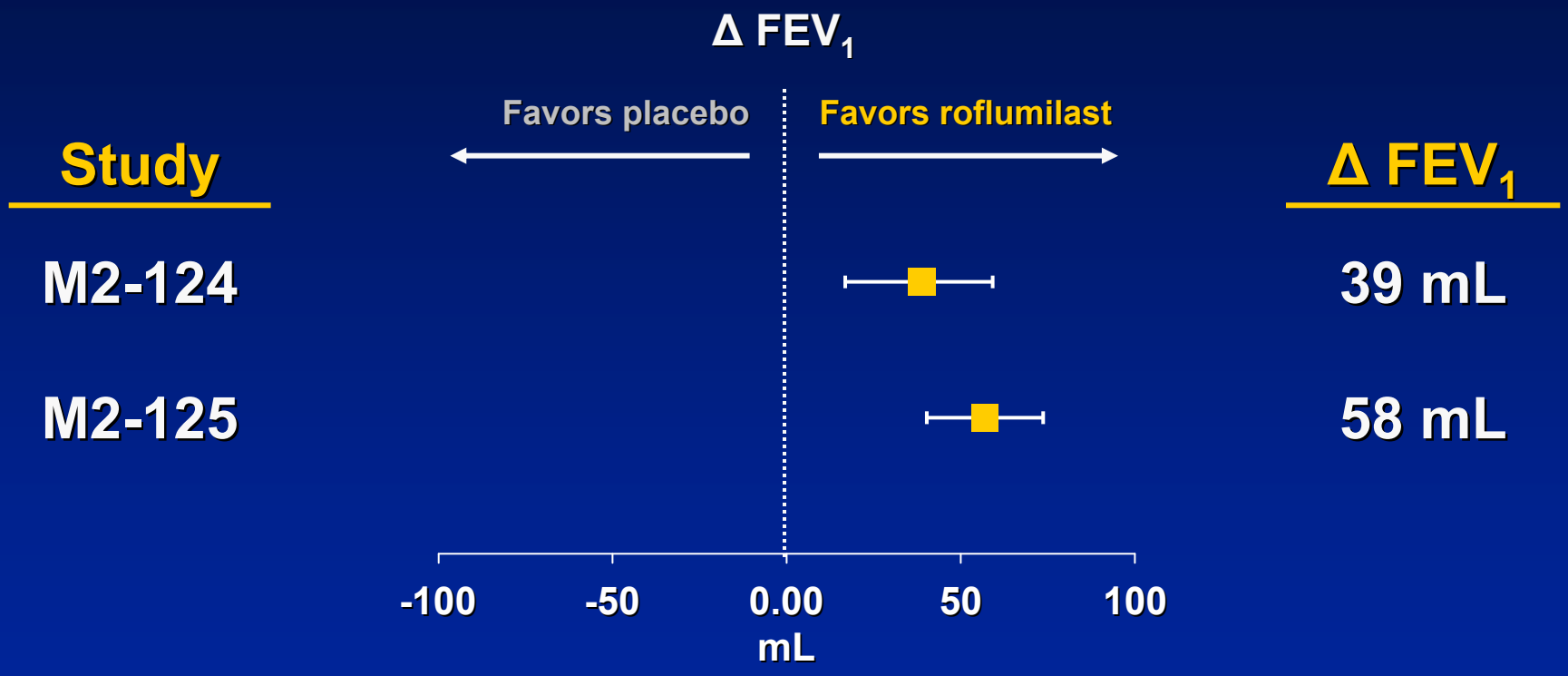
Concomitant Medication

	M2-124		M2-125	
	rof500 (N=765) (%)	placebo (N=758) (%)	rof500 (N=772) (%)	placebo (N=796) (%)
Concomitant treatment with long-acting β_2-agonists	49	51	48	51
Concomitant treatment with short-acting anticholinergics	31	32	39	41
Concomitant treatment with short-acting β_2-agonists	99	99	99	99

ITT Population

M2-124 / M2-125

Primary End Point: Significant Improvement in Pre-bronchodilator FEV_1

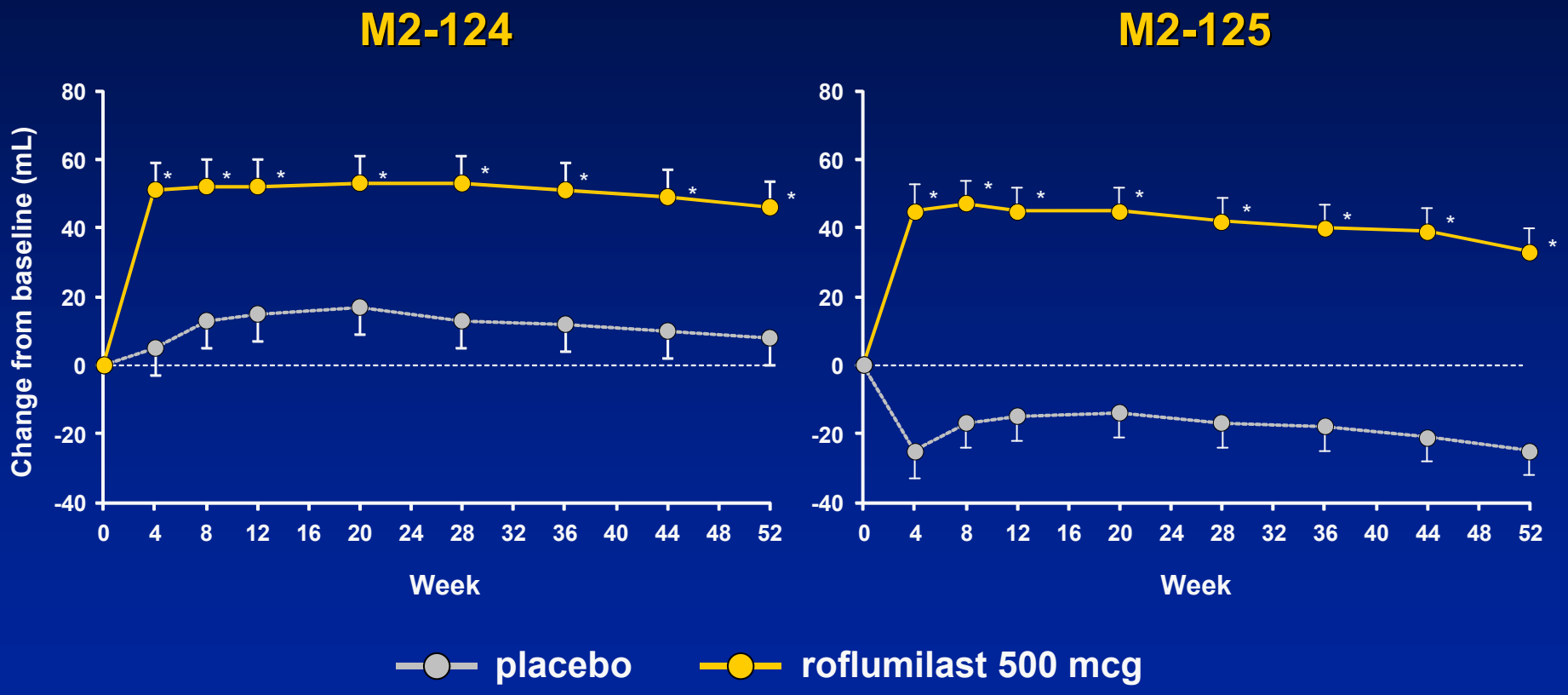


Repeated measure ANCOVA was used with unstructured covariance matrix to estimate mean. Means are adjusted for baseline measurements

Calverley, et al. Lancet, 2009.

M2-124 / M2-125

Sustained Improvements in Pre-bronchodilator FEV_1



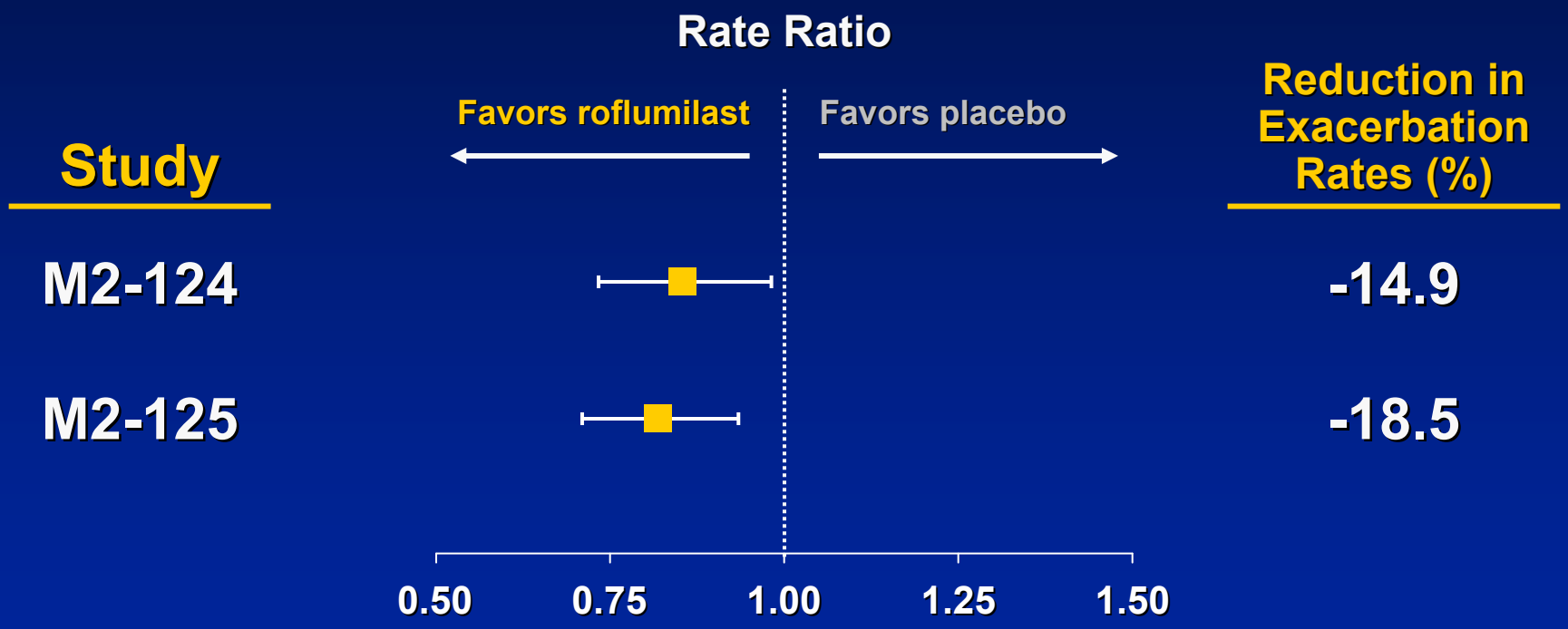
- **No indication of tolerance**

* Statistically significant; $p<0.05$

Calverley, et al. Lancet, 2009.

M2-124 / M2-125

Primary End Point: Significant Reduction in the Rate of Moderate or Severe COPD Exacerbations

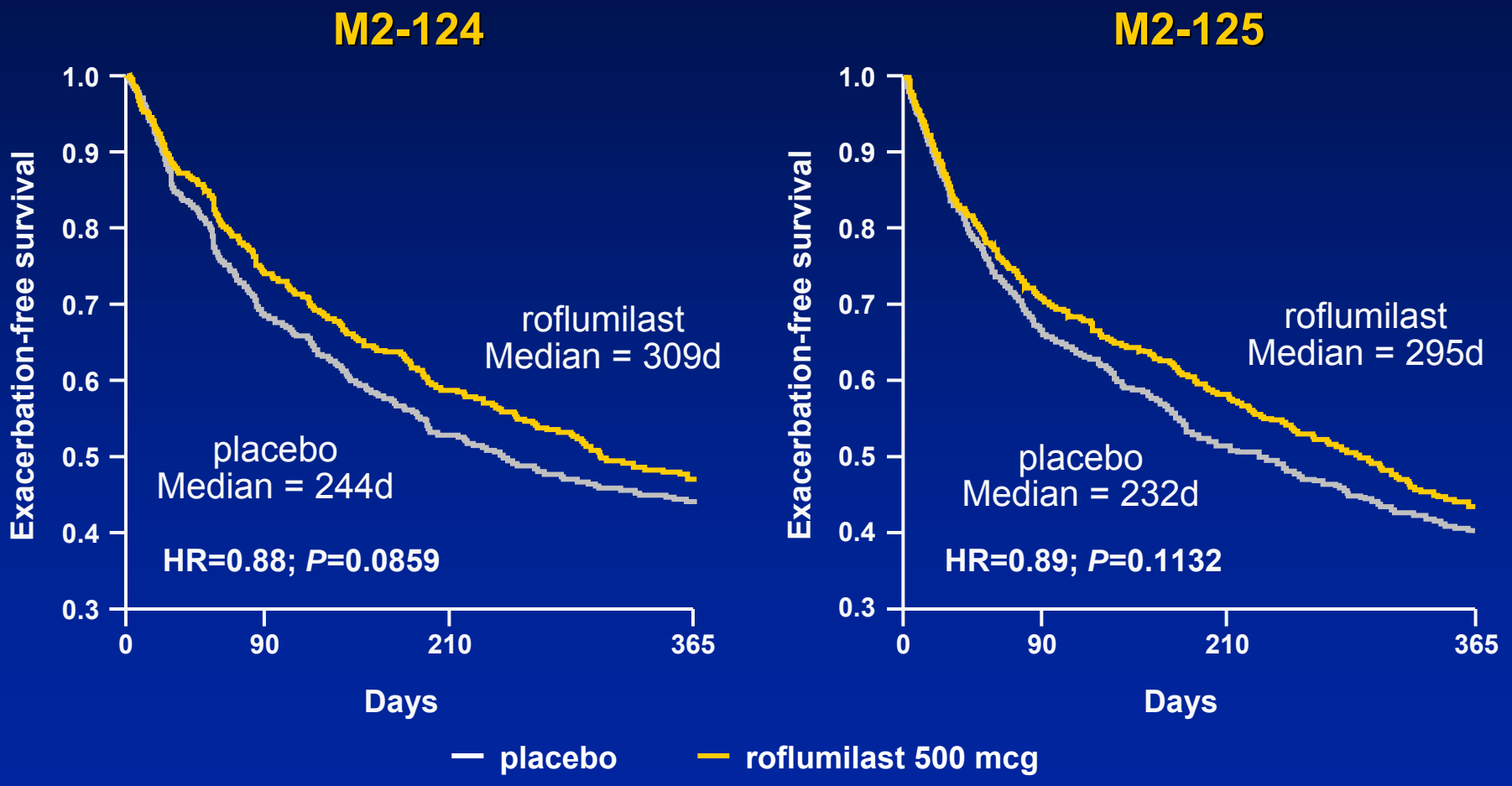


Exacerbation rates were based on a Poisson regression model corrected for treatment exposure and overdispersion

Calverley, et al. Lancet, 2009.

M2-124 / M2-125

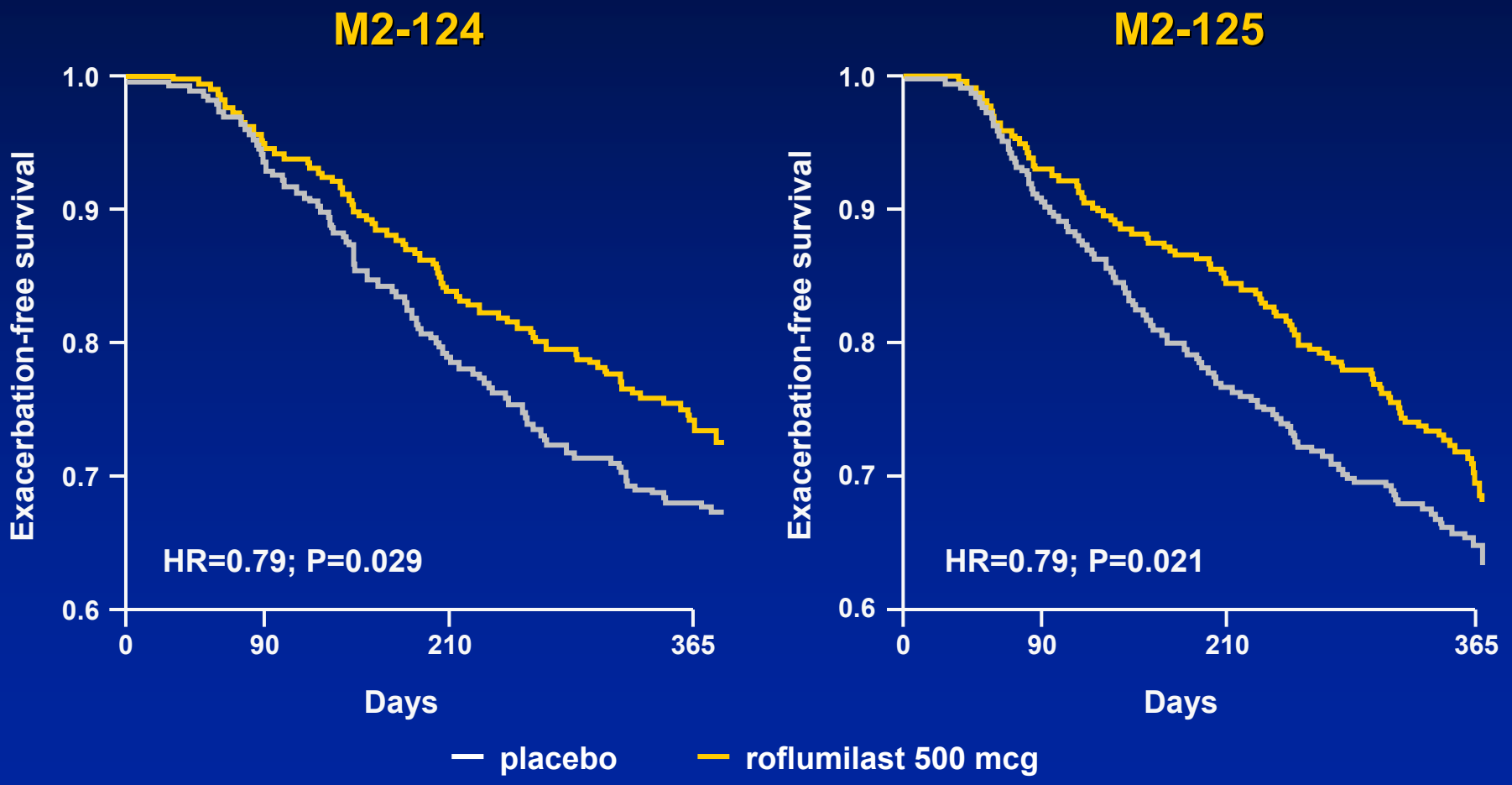
Increased Time to First Moderate or Severe Exacerbation Favors Roflumilast



Hazards ratio (HR) estimated using the Cox proportional hazards regression model.
(Kaplan-Meier Analysis, ITT)

M2-124 / M2-125

Significantly Prolonged Time to Second Moderate or Severe Exacerbation



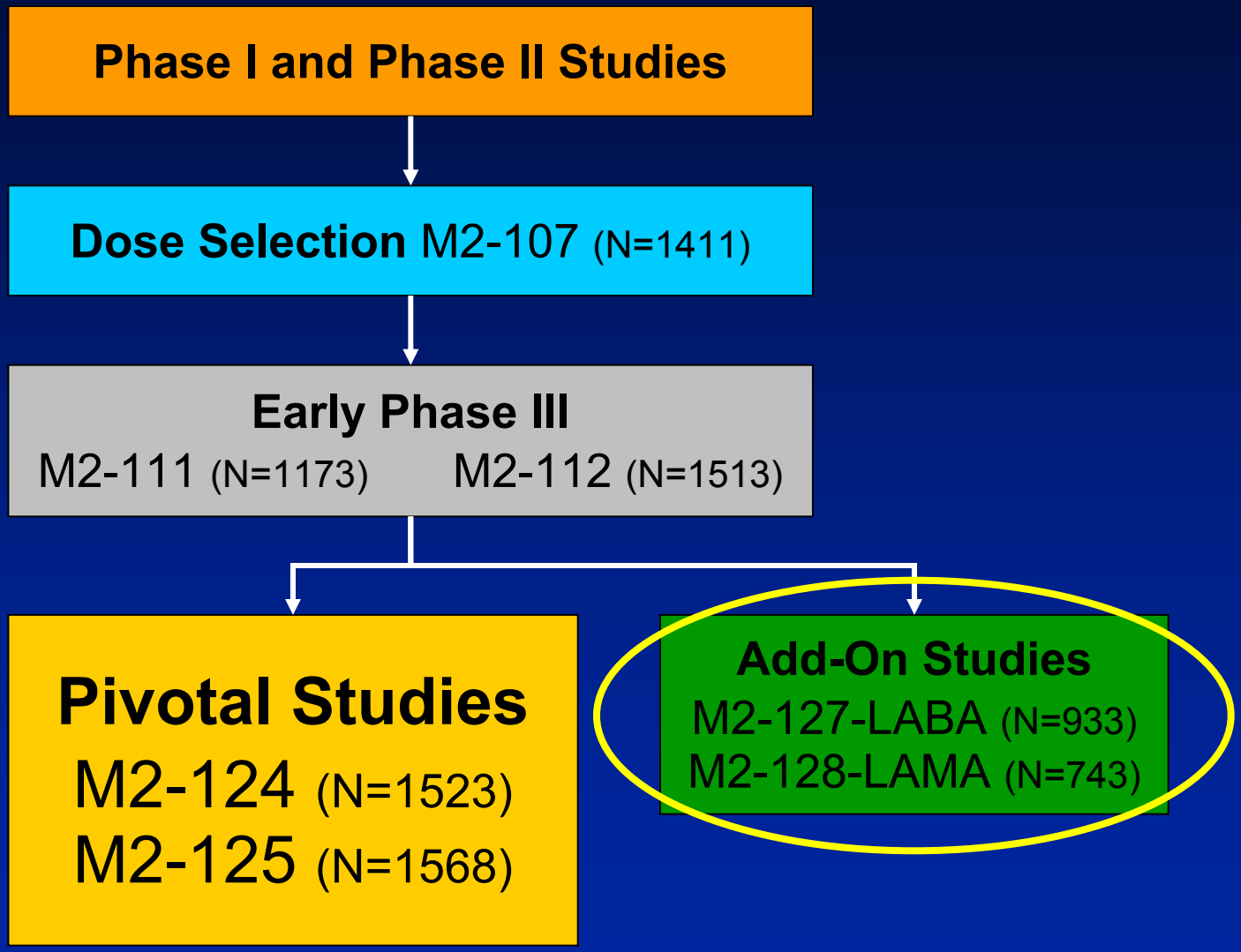
Hazards ratio (HR) estimated using the Cox proportional hazards regression model.
(Kaplan-Meier Analysis, ITT)

M2-124 and M2-125 Combined

Time to Each Moderate or Severe Exacerbation

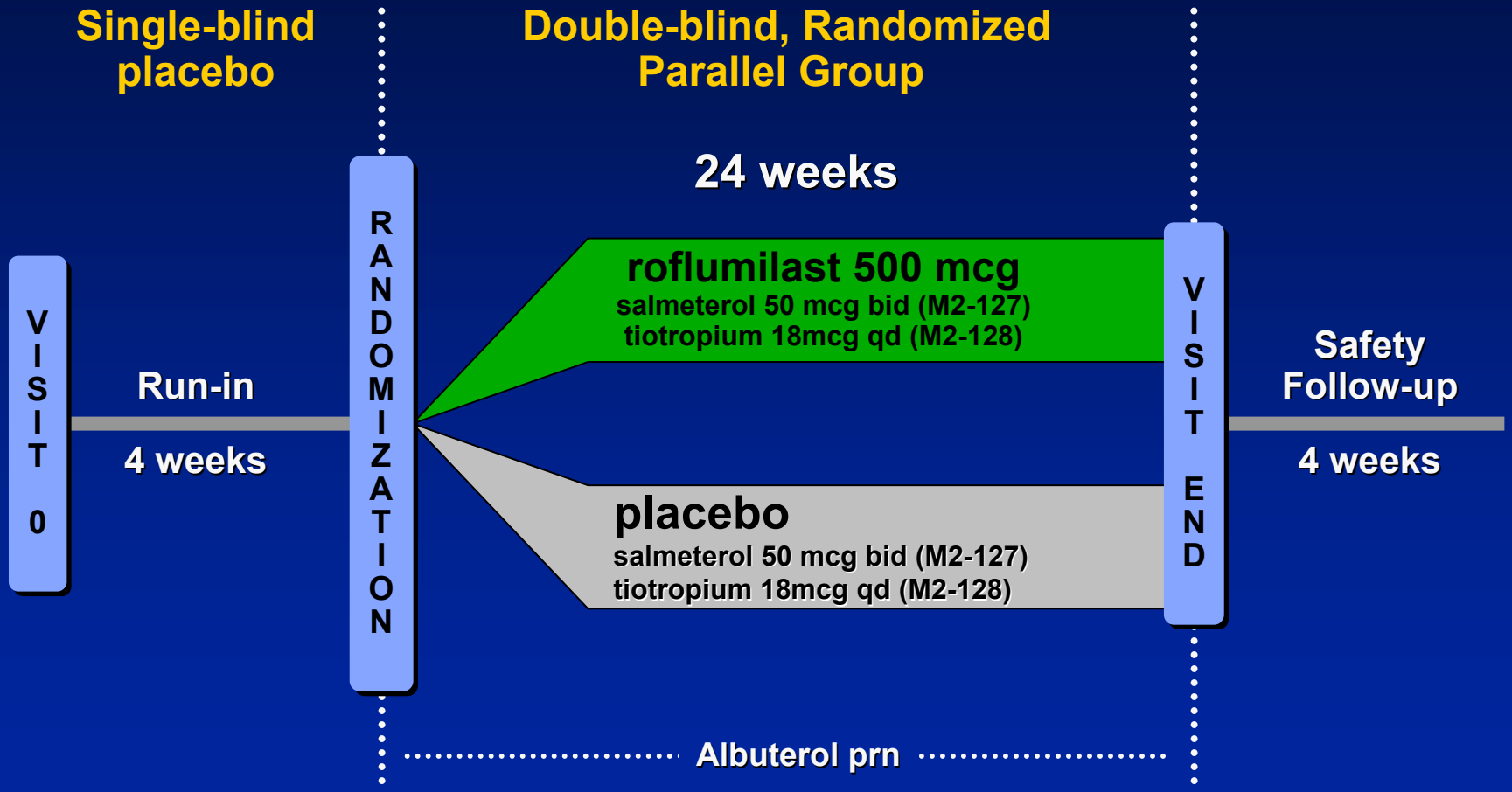
	Hazard Ratio	(95% CI)	No. of Exacerbations rof500 (N=1,537)	No. of Exacerbations placebo (N=1,554)
Time to 1st Exacerbation	0.89	(0.80, 0.98)	717	821
Time to 2nd Exacerbation	0.79	(0.69, 0.91)	329	430
Time to 3rd Exacerbation	0.73	(0.59, 0.90)	152	218
Time to 4th Exacerbation	0.60	(0.44, 0.81)	62	112
Time to 5th Exacerbation	0.48	(0.30, 0.76)	25	57
Total exacerbations			1,285	1,638

Roflumilast COPD Clinical Program



M2-127 / M2-128

Roflumilast Add on Studies: Salmeterol and Tiotropium



M2-127 / M2-128

Key Study Features

Moderate to Severe COPD

- Primary End Point: Pre-bronchodilator FEV_1
- FEV_1 40% to 70% predicted
- No ICS, SAMA, theophylline, or other long acting bronchodilator medications were allowed after study enrollment
- M2-127: Add on to salmeterol maintenance
- M2-128: Add on to tiotropium maintenance
  - Chronic bronchitis required
  - Frequent prn use of SABAs required

M2-127 / M2-128

Demographics and Baseline Characteristics (ITT Population)

	M2-127		M2-128	
	salmeterol + roflumilast (N=466)	salmeterol + placebo (N=467)	tiotropium + roflumilast (N=371)	tiotropium + placebo (N=372)
Median Age (years)	65	65	65	65
Men (%)	69	64	71	72
Cigarette pack-years	43	43	43	42
Current smoker (%)	40	39	40	39
Chronic bronchitis (%)	79	78	100	100
Use of as-needed relievers (median, range) puff/d	1.4 (0 to 17.1)	1.7 (0 to 28.7)	4.7 (0 to 20.0)	4.6 (1.0 to 36.3)

ITT population

M2-127 / M2-128

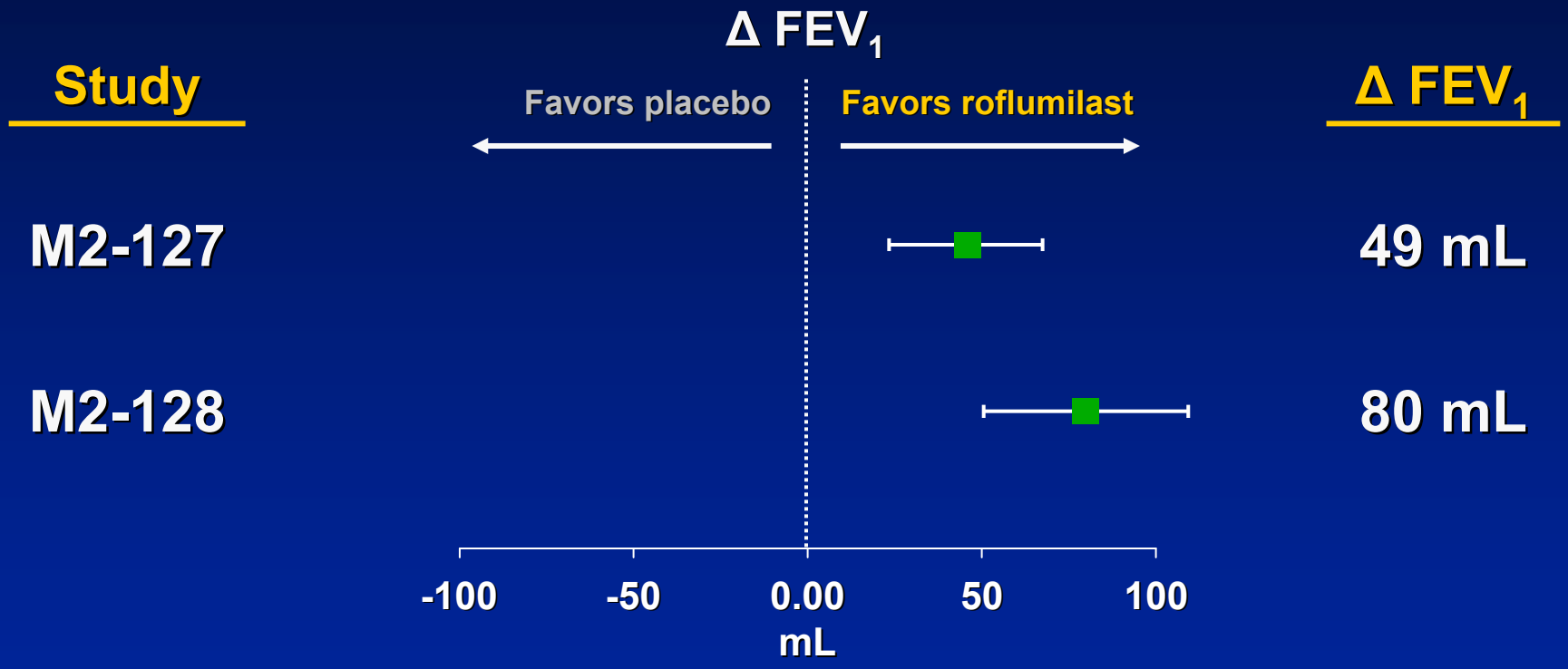
Demographics and Baseline Characteristics (ITT Population) *(cont.)*

	M2-127		M2-128	
	salmeterol + roflumilast (N=466)	salmeterol + placebo (N=467)	tiotropium + roflumilast (N=371)	tiotropium + placebo (N=372)
Pre-bronchodilator FEV_1 (L) (% predicted)	1.43 (52)	1.41 (52)	1.47 (53)	1.49 (53)
Reversibility (%)	6.2	6.4	5.9	6.0
Post-bronchodilator FEV_1/FVC (%)	50	50	53	52
Moderate COPD (%)	65	69	63	65
Severe COPD (%)	35	30	34	32

M2-127 / M2-128

Primary End Point: Significant Improvement

Pre-bronchodilator FEV_1



Repeated measure ANCOVA was used with unstructured covariance matrix to estimate mean. Means are adjusted for baseline measurements

Fabbri, et al. Lancet, 2009

M2-127 / M2-128

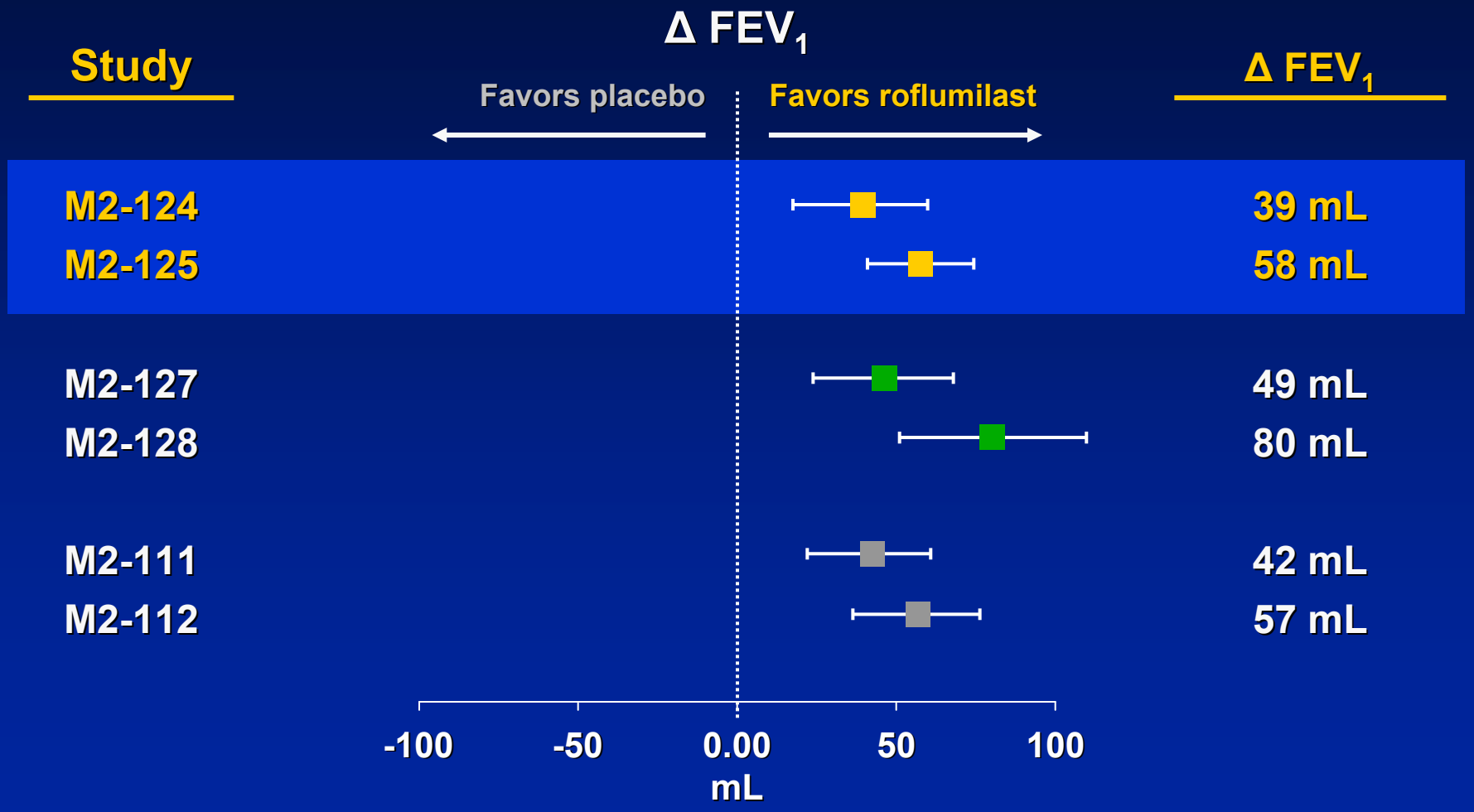
The Rate of Moderate or Severe COPD Exacerbations Favors Roflumilast

Exacerbation rates were based on a Poisson regression model corrected for treatment exposure and overdispersion

*Post hoc analysis M2-127

Fabbri, et al. Lancet, 2009

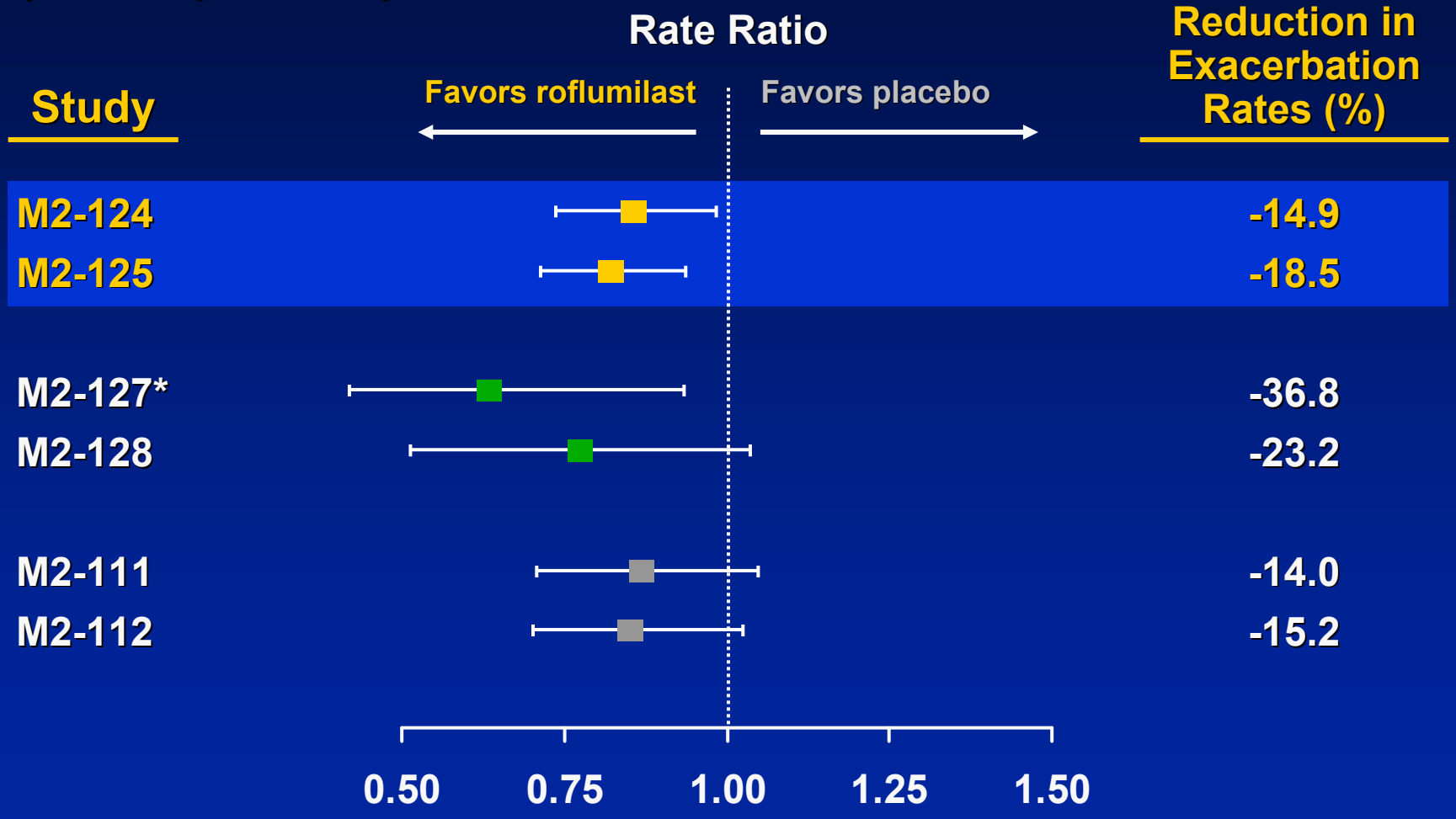
Consistent and Significant Improvement in Pre-bronchodilator FEV_1 Across Studies



Repeated measure ANCOVA was used with unstructured covariance matrix to estimate mean.
Means are adjusted for baseline measurements.

Consistent Reduction of Moderate or Severe COPD Exacerbations Favors Roflumilast

(ITT Population)



Exacerbation rates were based on a Poisson regression model corrected for treatment exposure and overdispersion.

*Post-hoc analysis

Summary of Clinical Efficacy

- Extensive COPD Clinical Program with more than 5,700 patients on 500 mcg qd
- Consistent results across studies for reduction of exacerbations and improvement in lung function
- Pivotal studies showed statistically and clinically significant improvements in both primary end points (FEV_1 and exacerbation rates)
- Sustained effects on FEV_1 and reduction of exacerbations
- M2-127 / M2-128 show improvement in lung function on top of both LABA and LAMA therapy
- Consistent demonstration of efficacy in well-documented COPD patients with bronchitic symptoms

Presentation Overview

Introduction	***Lisa Travis, MS, RAC*** Director, Regulatory Affairs Forest Research Institute, Inc.
Medical Need & Pharmacology	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Roflumilast Investigator
Dose Finding & Efficacy	***Klaus F. Rabe, MD, PhD*** Professor of Medicine, Department of Pulmonology Leiden University Medical Center Roflumilast Investigator
Safety	***Marco Taglietti, MD*** Chief Medical Officer Forest Research Institute, Inc.
Risk/Benefit & Clinician Perspective	***James Donohue, MD*** Chief of Pulmonary Medicine University of North Carolina, Chapel Hill Roflumilast Investigator

Safety

Marco Taglietti, MD

Chief Medical Officer
Forest Research Institute

Roflumilast Safety Assessment

- Safety Overview
  - Treatment Emergent Adverse Events (AEs)
  - Discontinuation due to Adverse Events
  - Serious Adverse Events (SAEs)
  - Deaths
- Events of Interest
  - Diarrhea
  - Pancreatitis
  - Weight Loss
  - Neuropsychiatric Events
  - Tumor Events
  - Cardiovascular Events

COPD Safety Pool Includes 14 COPD Placebo-Controlled Phase II/III Trials

	COPD Safety Pool		
Exposure	placebo	rof500*	rof250*
Number of Patients	5,491	5,766	797

- Significant long-term exposure with roflumilast
  - 1,232 patients treated for one year
  - 3,261 patient-years exposure
- No notable imbalances between treatments in demographics, concomitant medications and COPD severity

* rof500 = roflumilast 500 mcg; rof250 = roflumilast 250 mcg

Most Frequently Reported AEs

	COPD Safety Pool	
	placebo (N=5,491) (%)	rof500 (N=5,766) (%)
All AEs	62.8	67.2
COPD Exacerbations	23.1	19.8
Diarrhea	2.6	10.1
Weight Decreased	1.8	6.8
Nasopharyngitis	6.3	6.3
Nausea	1.4	5.2
Headache	2.0	4.6
Upper Respiratory Tract Infection	4.3	3.8
Bronchitis	3.5	3.1
Back Pain	2.1	3.1
Insomnia	0.9	2.6
Influenza	2.4	2.5
Dizziness	1.2	2.4
Decreased Appetite	0.4	2.2
Pneumonia	2.0	1.8

Discontinuations Due to Adverse Events

	COPD Safety Pool	
	placebo (N=5,491) (%)	rof500 (N=5,766) (%)
All AEs	**9.2**	**14.3**
Gastro-Intestinal AEs	**0.8**	**5.1**
Diarrhea	<0.1	2.5
Nausea	0.2	1.6
All Other AEs	**8.4**	**9.2**

Serious Adverse Events (SAE)

	COPD Safety Pool	
	placebo (N=5,491) (%)	rof500 (N=5,766) (%)
All SAEs	**14.2**	**13.5**
COPD Exacerbation	7.1	5.8
Pneumonia	1.1	1.1
Atrial Fibrillation	0.2	0.4
Myocardial Infarction	0.4	0.2
Chest Pain	0.3	0.2

AEs Associated with Death

	COPD Safety Pool	
	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)
All Deaths	**86 (1.6)**	**84 (1.5)**
AE Associated with Deaths*		
COPD	22 (0.4)	20 (0.3)
Pneumonia	10 (0.2)	9 (0.2)
Cardiac Arrest	1 (<0.1)	7 (0.1)
Acute Respiratory Failure	4 (<0.1)	6 (0.1)
Sudden Death	6 (<0.1)	4 (<0.1)

* Investigator reported

Overview

- No difference in overall number of SAE
- No difference in overall number of Deaths
- 5% difference in AE discontinuations driven by GI events

Events of Interest

- Diarrhea
- Pancreatitis
- Weight Loss
- Neuropsychiatric Events
- Tumor Events
- Cardiovascular Events

Diarrhea

- 16 Diarrhea SAEs in COPD Safety Pool
  - 3 cases before start of treatment

	COPD Safety Pool		
	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)	rof250 (N=797) n (%)
All Diarrhea AEs	143 (2.6)	585 (10.1)	39 (4.9)
Reported as SAEs	1 (<0.1)	10 (0.2)	2 (0.3)
SAE Recovered	1	10*	2

* 7 cases recovered without discontinuing the study and continued roflumilast treatment

Pancreatitis

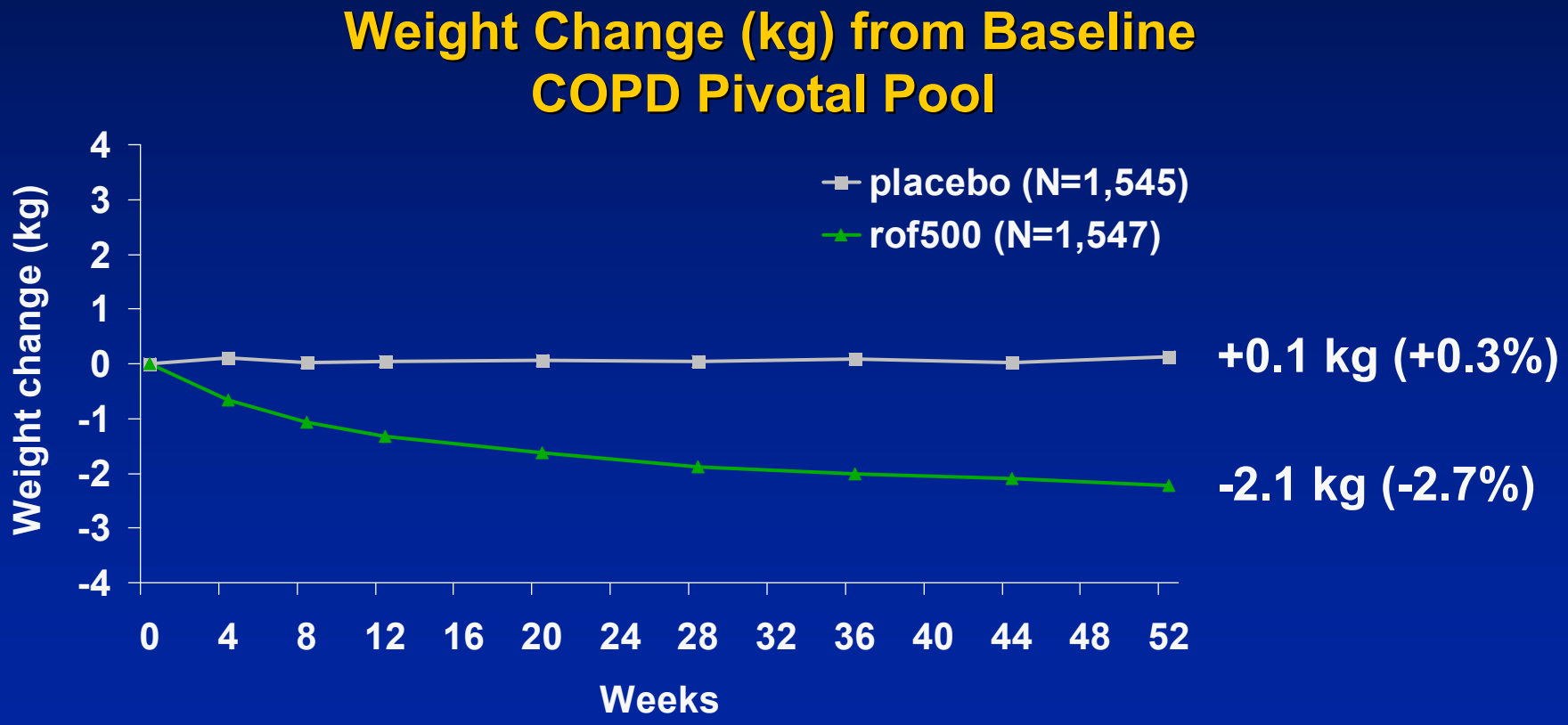
- No pre-clinical signal
- 16 Pancreatitis in COPD Safety Pool
  - 2 cases before starting treatment

	COPD Safety Pool		
	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)	rof250 (N=797) n (%)
All Pancreatitis Cases	7 (0.1)	6 (0.1)	1 (0.1)
Reported as SAEs	6 (0.1)	6* (0.1)	1 (0.1)
SAE Recovered	6 (0.1)	5 (0.1)	–
Associated with Death	–	1 (<0.1)	1 (0.1)

* 4 cases recovered without discontinuing the study and roflumilast treatment was continued

Weight Loss

- Weight loss assessed systematically in the COPD pivotal studies (M2-124 and M2-125)



Weight Change from Baseline by Sub-Groups

	COPD Pivotal Pool					
	placebo (N=1,545)			rof500 (N=1,547)		
	n	Δ Kg	(Δ %)	n	Δ Kg	(Δ %)
COPD Severity						
Moderate COPD	116	**0.1**	**(0.1)**	126	**-1.9**	**(-2.4)**
Severe COPD	972	**0.1**	**(0.1)**	927	**-2.1**	**(-2.7)**
Very Severe COPD	417	**0.0**	**(0.0)**	444	**-2.2**	**(-3.1)**
BMI						
Obese (>30 BMI)	316	**-0.5**	**(-0.5)**	317	**-3.6**	**(-3.7)**
Overweight (>25 ≤30)	462	**0.1**	**(0.1)**	475	**-2.0**	**(-2.6)**
Normal (>18.5 ≤25)	605	**0.1**	**(0.2)**	572	**-1.6**	**(-2.6)**
Underweight (≤18.5)	127	**1.3**	**(2.8)**	134	**-0.7**	**(-1.6)**

Safety Profile in Underweight Patients

	COPD Pivotal Pool (Underweight BMI ≤18.5)	
	placebo (N=126) n (%)	rof500 (N=131) n (%)
AEs	78 (62)	86 (66)
SAEs	26 (21)	24 (18)
Deaths	6 (4.8)	6 (4.6)

Additional Analyses

- Bioimpedance sub-study in M2-128
  - Weight decrease is due mostly to a loss of body fat
- AE and exacerbation analysis by weight loss
- Assessment of reversibility
- Effect of GI AEs on weight loss
  - Modest difference between patients with GI events (-2.6 kg) or without (-2.0 kg)
- Results from COPD Safety Pool are comparable to the COPD Pivotal Pool

Weight Change Summary

- Weight loss occurs more frequently with roflumilast
- Largest weight loss in obese patients but occurs also in underweight patients
- Mainly loss of fat mass based on bioimpedance data
- Evidence of reversibility after treatment discontinuation
- No increased morbidity due to weight loss was observed in comparison to placebo
- Patients and physicians should be informed that weight loss is associated with the use of roflumilast, and weight should be regularly monitored

Neuropsychiatric Observations – AEs

	COPD Safety Pool	
	placebo (N=5,491) (%)	rof500 (N=5,766) (%)
Psychiatric disorders	**3.0**	**6.0**
Insomnia/Sleep disorder	1.1	3.0
Anxiety/Anxiety disorder	0.8	1.4
Depression/Mood change	0.8	1.4
Nervous system disorders	**5.5**	**10.7**
Headache	2.0	4.6
Dizziness	1.2	2.4
Tremor	0.3	1.7

Similar Rates of Neuropsychiatric SAEs

Serious Adverse Events	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)
Nervous system disorder	44 (0.8)	37 (0.6)
Psychiatric disorders	13 (0.2)	12 (0.2)

Psychiatric Observations – Patients With Suicidal Behavior

	COPD Safety Pool		
	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)	rof250 (N=797) n (%)
Suicide attempt	–	2 (0.03)	–
Suicidal ideation	1 (0.02)	–	–
Completed suicide			
While on drug	–	1 (0.02)	–
>20 days after discontinuation	–	1 (0.02)	1 (0.13)

- No additional suicidality cases detected by blinded C-CASA Adjudication

C-CASA: Columbia-Classification Algorithm Suicide Assessment

Suicide Behavior Assessment

Completed Suicides

1. **Rof500:** M/80y, 17 wks on rof500, no history of depression, reserpine as concomitant medication, completed suicide while on drug
2. **Rof500:** M/76y, 11 days on rof500, patient-reported depression on Euro-QoL at baseline, completed suicide 22 days after last dose, SNRI for 10 days before suicide
3. **Rof250:** M/73y, 16 wks on rof250, no history of depression, suicide 20 days after last dose

Attempted Suicides

1. **Rof500:** F/50y, 11 months on rof500, history of depression, concomitant antidepressant
2. **Rof500:** F52y, 5 months on rof500, history of depression and attempted suicide, continued treatment with rof500 until end of study

Suicidal Ideation

1. **Placebo:** F/48y, 2 weeks on placebo, history of depression with multiple concomitant antidepressants. Hospitalization for severe depression and persistent suicidal ideation.

Neuropsychiatric Conclusions

- Higher incidence of adverse events in the roflumilast group
  - Primarily Insomnia and Anxiety
- No difference in SAEs compared to placebo
- 5 suicidal behaviors (including 3 completed suicides) with roflumilast vs 1 placebo
  - Event rate too low to draw a conclusion about association
- Physicians and Patients should be informed of the higher incidence of neuropsychiatric events including rare events of suicidal behavior
- Patients should be monitored for changes in neuropsychiatric events

Tumor Events – Preclinical Findings

- Carcinogenicity studies (mice and hamsters)
  - No increases in drug related tumors in mice
  - Isolated increase in nasal/olfactory tumors in hamsters
- Rodent specific mechanism for nasal tumors

	Exposure Margins for Humans			
	Mice		Hamsters	
Exposure margins (fold) of ADCP N-oxide at which no other tumors were observed	Plasma	Urine	Plasma	Urine
	109	704	153	682

- No concern for tumors based on nonclinical carcinogenicity data

Tumor Events – Frequency

- 208 Patients with 218 tumors in the Total Safety Database
  - 10 Subjects with two tumors (6 on placebo and 4 on roflumilast)
  - 1 Subject in Phase I and 1 Patient on active control group

	placebo	roflumilast
Safety Pool	n/N (%)	n/N (%)
All COPD/Asthma Studies	80/8260 (1.0)	126/13216 (1.0)
COPD Safety Pool	72/5491 (1.3)	98/6563 (1.5)
COPD Other	5/249 (2.0)	20/900 (2.2)
Asthma Studies	3/2520 (0.1)	8/5753 (0.1)

Frequency of Specific Tumor Events

	COPD Safety Pool		
	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)	rof250 (N=797) n (%)
All Tumors	72 (1.3)	94 (1.6)	4 (0.5)
Lung Cancer	17 (0.3)	31 (0.5)	2 (0.3)
Prostate Cancer	7/3979 (0.2)	13/4158 (0.3)	1/585 (0.2)
All Other Cancers	48 (0.9)	50 (0.9)	1 (0.1)

- Higher distribution of some tumors in initial months of exposure
  - e.g. 22 lung cancers in roflumilast vs 6 in placebo in the first 6 months
- Comparable incidence to general COPD population

Tumor Events Conclusions

- No relevant preclinical carcinogenicity signal
- Similar incidence in the total safety database
- Tumors, mostly solid, reported early in study for roflumilast
  - Biological implausibility for early tumors
- No evidence of increased risk of tumors

Cardiovascular Assessment

- No pre-clinical concerns for cardiac toxicity or conduction abnormalities
- TQT at doses up to 1,000 mcg showed no QTc prolongation signal
- Holter monitoring did not show any difference between roflumilast and placebo (n=210)

Blinded Adjudication of All-Cause Mortality

- All deaths adjudicated by a blinded panel of three independent experts
  - None of the panelists were roflumilast investigators
- Fatal events allocated into three main groups
  - Cardiovascular
  - Non-cardiovascular
  - Insufficient data
- If disagreement in the independent reviews, Chair met with the panel to reach consensus

No Increased Risk for Cardiovascular Mortality

	COPD Safety Pool	
	placebo (N=5,491) (n=86*)	rof500 / rof250 (N=6,563) (n=91*)
	n (%)	n (%)
Cardiovascular	**42 (0.7)**	**35 (0.5)**
Sudden Death, Etiology Unknown	26 (0.4)	22 (0.3)
Death Due to Myocardial Infarction	3 (<0.1)	4 (<0.1)
Death Due to Stroke	4 (<0.1)	3 (<0.1)
Sudden Death Due to Arrhythmia	2 (<0.1)	1 (<0.1)
Death Due to Congestive Heart Failure	4 (<0.1)	2 (<0.1)
Other Cardiovascular Deaths	3 (<0.1)	3 (<0.1)
Non-cardiovascular	**40 (0.7)**	**52 (0.8)**
Insufficient Data	**4 (<0.1)**	**4 (<0.1)**

* Number of Deaths

Conclusions

- Well characterized safety profile in a large database
- Diarrhea and Nausea more common with roflumilast
  - Mostly mild to moderate, reversible, with no relevant sequelae
- Weight loss is associated with use of roflumilast
  - Weight monitoring is recommended
- Neuropsychiatric events
  - Higher reporting rate (including rare events of suicidal behavior) with roflumilast compared to placebo
  - Physician should be alert for any change in neuropsychiatric events in their patients
- No evidence of increased risk for Cardiac Events, Pancreatitis, Tumors and Infections
- Forest committed to patient safety and to implementation of appropriate risk management activities

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Safety	***Marco Taglietti, MD*** Chief Medical Officer Forest Research Institute, Inc.
Risk/Benefit & Clinician Perspective	***James Donohue, MD*** Chief of Pulmonary Medicine University of North Carolina, Chapel Hill Roflumilast Investigator

Risk/Benefit & Clinician Perspective

James Donohue, MD

Chief of Pulmonary Medicine
University of North Carolina, Chapel Hill

Roflumilast Investigator

There is pressing need to develop new drugs for COPD...

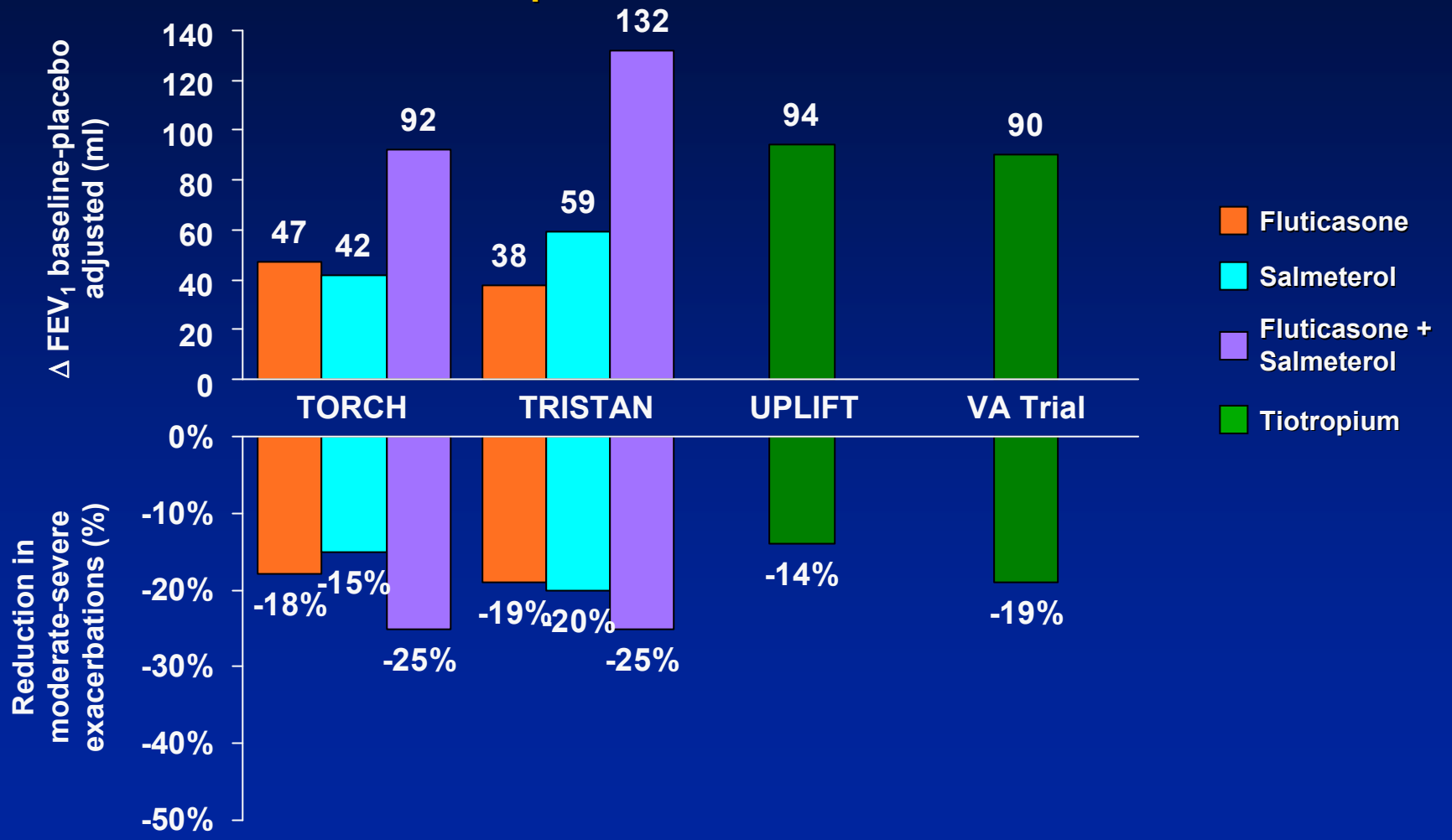
FDA 2007 Draft Guidance for Industry

"Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment"

Issues Raised by the Division

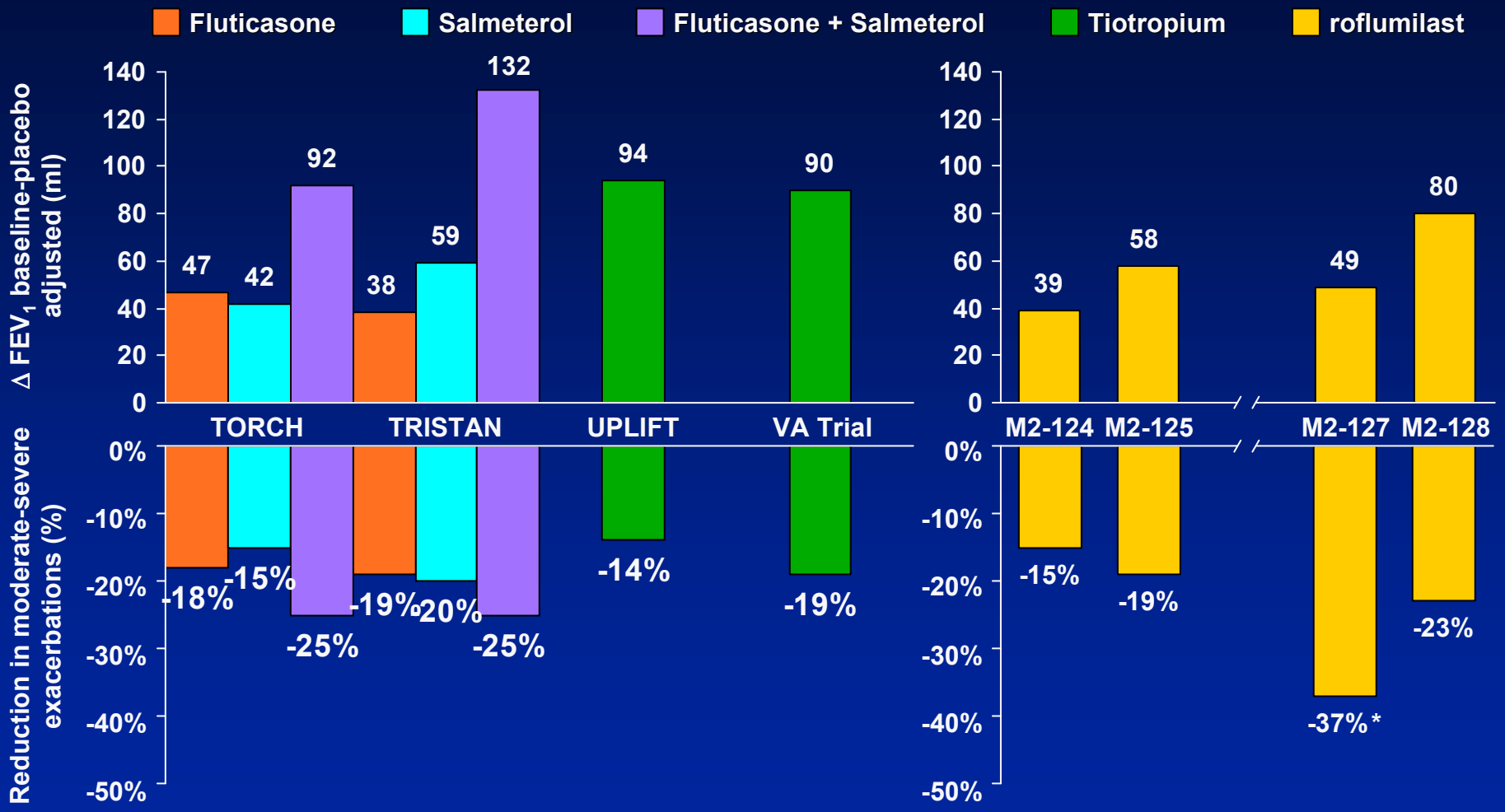
- Relevance of FEV_1 changes
- Consistency and persistence of effects
- Findings relative to US COPD population
- Definition of exacerbation

Effect Size in Large Placebo-controlled Studies of Approved Therapies for COPD Exacerbation Reduction and FEV_1



Niewoehner et al, Ann I med 2005; Tashkin et al, 2008; FDA Spiriva Briefing Book November 2009 Anzueto et al J COPD 2009; Ferguson et al Resp Med 2009: Calverley et al LANCET 2003 ; Calverley et al NEJM 2007

Effect Size of Roflumilast in Context of Approved Therapies



* Post hoc analysis

Niewoehner et al, Ann I med 2005; Tashkin et al, 2008; FDA Spiriva Briefing Book November 2009 Anzueto et al J COPD 2009; Ferguson et al Resp Med 2009: Calverley et al LANCET 2003; Calverley et al NEJM 2007

Benefit / Risk Conclusions

Benefits

- Target population identifiable
- Consistent Efficacy in reducing exacerbations and improving lung function
- Additive
- New mechanism of action
- Once a day oral tablet

Risks

- Adverse event rates similar to other commonly prescribed drugs for chronic use
- Most adverse events mild to moderate intensity
- Weight loss manageable
- Changes in mood and behavior should be monitored

Where Would I Use Roflumilast?

- Chronic bronchitis
- Risk of exacerbation at least within the last 12 months
- Poor lung function
- Add on to Bronchodilator